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CONTENTS

Editorial

The indispensable relevance of qualitative research in day-to-day clinical practices

Qualitative research serves as an investigative approach designed to comprehend social phenomena within their natural contexts, seeking insights into individuals' experiences, perceptions, and behaviors. This method of research is important for understanding the human aspects of healthcare, as it helps healthcare professionals learn about the experiences, views, and feelings of both patients and caregivers.[1,2] This method has a long history of studying human social behavior and cultures, with a growing and strong base of evidence. In healthcare, clinical practices are usually based on evidence-based medicine, which means that decision-making depends a lot on scientific research.[3,4] This editorial endeavors to underscore the significance of qualitative research within clinical settings, emphasizing its positive influence on enhancing patient care and overall healthcare outcomes.

A key strength of qualitative research lies in its capacity to unveil the subtleties and contextual elements influencing patient care. For instance, it can illuminate the social, cultural, and economic factors that might impact a patient's adherence to treatment, their pain experience, or their decision-making processes.[3,5] These nuanced insights are crucial for healthcare providers in crafting tailored interventions and strategies that better align with the distinct needs of each patient. Moreover, qualitative research allows healthcare professionals to explore intricate issues that may not be easily addressed through quantitative methods.[4,6,7] It offers an understanding of the psychosocial repercussions of chronic illnesses, the experiences of marginalized populations, and the emotional complexities of medical decision-making. Through a grasp of these intricate matters, healthcare providers can deliver more compassionate and effective care, ultimately leading to improved patient outcomes.[8,9]

Qualitative research serves as a valuable tool for gaining insights into the experiences and perceptions of patients, enabling healthcare professionals to customize their care to better align with patient needs. Additionally, it aids in identifying obstacles to care, such as language, cultural, or financial barriers, empowering healthcare providers to formulate targeted interventions to address these challenges effectively.[9,10] This approach proves instrumental in developing clinical guidelines and protocols, ensuring their relevance and efficacy for the specific target population. Various methodologies, including interviews, observations, and focus groups, are employed to collect comprehensive and in-depth qualitative data. By delving into the lived experiences of patients, qualitative research contributes to a more thorough understanding of the human aspects of healthcare.[11]

Qualitative research is crucial for healthcare, as it adds the necessary context that improves clinical choices. Quantitative data reveals the symptoms and outcomes, but qualitative data shows the human aspects and realities that numbers cannot capture. This approach of research listens to patients' stories and expresses them. It helps us understand how social factors like poverty, discrimination, and lack of health support affect them. This method helps us learn about their views, aspirations, and challenges during their sickness journey. We can empathize and connect with them better by seeing their point of view, leading to a more comprehensive understanding of healthcare.[3,11]

This level of comprehension has real-world ramifications. Equipped with an understanding of the social variables that shape a community, we may design public health initiatives that have a greater effect. Increased knowledge in adherence counseling is made possible by learning from patients' experiences with medications. Setting attainable goals is made easier by having an understanding of lifestyle obstacles. Understanding people's emotional journeys helps for compassionate end-of-life discussions. Qualitative research not only affects the treatment of individual patients but also has a significant impact on the development of the larger healthcare system. It provides data for advocacy campaigns, organizational reform, and policy creation.[9,12]

Qualitative research is important and beneficial for healthcare, but it faces some difficulties, such as the large amount of time and resources required for collecting, analyzing, and interpreting data. However, these difficulties should not stop healthcare professionals and researchers from using this method. Working together, having diverse research teams, and using resources wisely can solve these problems, making qualitative research easier to

use in daily clinical practices. While quantitative studies give useful numerical insights, qualitative research helps to understand the human factors of healthcare better, improving practitioners' ability to understand, relate, and provide holistic care.[13]

Qualitative research can improve the communication and trust between healthcare providers and patients, creating stronger bonds. By paying attention to patients' stories and views, communication can be better, trust can be higher, and patient outcomes can be improved.[13,14] Beyond informing practice, qualitative research plays a critical role in several areas:

- **Generating New Research Questions**: By uncovering unseen patterns and identifying areas where quantitative data falls short, qualitative research sparks new avenues for investigation.
- **Developing and Improving therapies:** Qualitative research facilitates the iterative development and improvement of therapies, guaranteeing that they are viable in real-world settings, culturally sensitive, and meet patient requirements.
- **Assessing the Impact of the Intervention**: To gain a more profound knowledge of the lived experiences of study participants, qualitative techniques are used in addition to quantitative assessments. Incorporating qualitative research into day-to-day clinical practice requires a shift in perspective and collaboration between researchers and clinicians.[11]

This cooperative strategy could lead to:

- **Increasing Patient Satisfaction**: Better health outcomes result from attending to each patient's wants and preferences, which also increases patient happiness.
- **Maximizing the Use of Resources**: Effective and fair resource allocation is influenced by an understanding of the variables impacting healthcare decision-making.
- **Developing Qualitative Research Skills in Healthcare Professionals**: This allows for the critical assessment of the available data, the adoption of best practices, and the promotion of patient-centered care.[14-16]

It's critical to understand that qualitative research is a complementary technique that offers an alternative viewpoint rather than a substitute for quantitative research. Healthcare may advance toward a future of truly patient-centered, evidence-informed care by accepting its significance and incorporating its lessons into clinical practice.[5,16]

In conclusion, we must recognize and value the invaluable role that qualitative research plays as we manage the complexity of modern healthcare. Qualitative research offers a rich tapestry of human experiences that goes beyond statistics. A more compassionate, patient-centered, and holistic healthcare system—one that promotes well-being in addition to curing illnesses—is fostered by incorporating these ideas into patient care. In support of more integration of qualitative research into clinical decision-making and patient care, this editorial exhorts medical practitioners to value it.

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Review Article

Medical professionals as victims of human rights violation

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Abstract

Medical practice has changed a lot with the passage of time. The concept of an ideal human being in the form of a doctor is rare nowadays. This evolution is obvious, so as to keep pace with the modern society. The principles of Medical Ethics still holds good in today's world, but certain modifications are necessary. The idea behind these principles is to safeguard the interest of the patient. With the rapid spread of digital technology, access to the internet and social networking the face of doctor patient relationship has gained a new dimension. The patient enjoys his autonomy and has the scope of verifying and cross examining the physician regarding the treatment. The principle of non-maleficence implies that the doctor will do no harm to the patient even if he is unable to provide treatment that is, beneficial for the patient. But does the same principle hold good for the patient too? If the patient is not satisfied with the treatment he has the right to lodge complaint against the physician and frame charges of medical negligence. This act does not conform to the principle of non-maleficence on the part of the patient. Moreover the lack of autonomy for the doctor and the mental stress of litigations constitute violation of human rights for the practitioners. Hence abiding by the principles of medical ethics may lead to victimization of human rights violation. The Principles of "Dignity" and "Unity" need to be incorporated in view of the present scenario and changing trends in medical practice.

Keywords: Ethics, human rights, medical practice, violation

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INTRODUCTION

Medical profession is considered to be a noble profession even today. There was a time when doctors were considered to be next to god. But times have changed. Keeping in pace with the ever changing society, outlook of the common man has changed a lot. The advent of new technologies and influence of social media at large has had its impact on the society. Faith on medical practitioners is losing its ground to internet-based knowledge of the patients. The moral and ethical values of the society are attaining new dimensions. The dispute whether such change in the moral values are good or bad will always remain, but the fact is that, it is being accepted by the present generation. The concept of "good" or "bad" is never absolute. It is always a relative term based on the social environment, customs, and norms.

Medical professionals are also part of this evolving society. The budding doctors are also being exposed to the same cultural and social changes. The society drifts with the changes of the new era but is not ready to accept such changes for its doctors. Ironically, the expectations of the common man from a physician still revolve around the age old concept of idealistic, noble human being—"a healer

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of the society," when the new generation of physicians have already modified themselves and adapted to the social evolution. In the present era of consumerism, changes in the ethics and morality are not restricted to the patient and their family members but also to the doctors. The society needs to accept such changes even if there are criticisms. It is high time we need to rethink about the ethical principles of medical practice.

ETHICS AND HUMAN RIGHTS

Our society always speaks of protection of human rights of its citizens. These are rights inherent to all human beings. They include "the right to life and liberty, freedom from slavery and torture, freedom of opinion and expression, right to work, and education" etc. Violation of any of these rights amounts to offence in our society. These are applicable to every citizen of the nation irrespective of their gender, race, religion, or profession. The media and organisations of social justice often raise their voice to safeguard the human rights of a convicted prisoner or even on the issues of dignity of a dead body, but seldom do we hear to protect the dignity of medical professionals. The right to practice medicine and provide service to the society without any threat, force or compulsion are the basic human rights of the practitioner. Baseless allegations of medical negligence, violence against doctors and constant threat of claims and compensation vitiate the mental peace of the physicians. Are these not violation of human rights against the doctors? The continuous and intense stress of being sued for any mishap hinders his freedom to practice in a liberal manner. It is no less than mental torture to the health care provider. However, it is pertinent to mention that professional malpractice by a section of doctors is an important reason for the change of perception of the society towards the profession. Nevertheless it is unjustified for the dignity of the whole doctor community to be maligned due to the unprofessional acts of few. There are adequate legal provisions for punishment of the defaulting professionals.

The pillars of medical ethics are autonomy, justice, beneficence, and non-maleficience.[1,2,3] These moral principles guide the medical practitioners in their practice and while dealing with their patients. However, there are no ethical principles to safeguard the rights of a doctor. Autonomy implies that every individual should have the power to take rational decisions and make moral choices and should be allowed to exercise her right regarding the decision.[4] But, is autonomy applicable only for the patients? In the era of digitalisation, the evidence-based medical practice has shifted from the Health Care Provider to the service recipient. Patients are eager to verify every treatment modality advised by the doctor and to cross examine the physician with limited knowledge gained from the internet. Are these not instances of interfering into the autonomy of the doctor? Should violation of autonomy not constitute violation of human rights of the practitioner on the grounds of limiting his freedom of work? Autonomy for the patient ensures his right to choose the modality of treatment. There may be situations where due to financial or other constraints a patient may choose a specific mode of treatment which might not be preferred by the doctor. However during treatment of such a case if there is a mishap the doctor is held liable for damages and compensations are claimed. Is it justified to hold the doctor liable in such a case? Where lies the autonomy of the doctor?

To safeguard the interests of the patient the rights and privileges of the patients have been framed. It is well known that the patient has the right to choose his doctor, to be treated with dignity as well as lodge a complaint in case he is not satisfied with the service provided. But that does not justify the acts of the patient or his family members to sue a doctor driven by emotional instincts resulting from an unintentional damage. In a study conducted by a government panel to investigate medical negligence cases in a state in India, it was found that out of the 112 cases filed for negligence in a year only 16 patients were the real victims of medical negligence that accounts for a little over 14%.[5]

Medical ethics speaks of Non-maleficence—"do no harm." This principle upholds several moral rules—do not cause pain or suffering, do not cause offence or do not deprive others of the goods of life.[6] During the course of treatment there may be situations where the prognosis of the patient may not be favourable. The physician knowing well about the outcome of the treatment tries to alleviate the pain and sufferings of the patient. If he is unable to provide any benefit atleast he makes sure that he does no harm to the sufferer. On the contrary the aggrieved family members in a situation of mental agony may fail to appreciate the efforts of the doctor. Dissatisfied with the outcome they often frame complaints of medical negligence. Does the principle of non-maleficeince not hold good for the relatives of the patient? No medical practitioner expects any compliments for their futile efforts. Atleast they deserve not to be harmed obeying the principle of non-maleficience. Such unwanted charges of negligence also constitute violation of the basic rights of the doctor in terms of mental torture and violation of his liberty for treatment decisions. As per Article 21

of the Constitution of India, "Right to life" has a wider meaning which includes the right to live with dignity. Doctors and healthcare workers also have the right to live with dignity under the same law.[7]

It is true that there are legal provisions for defending oneself in case of charge of negligence. The burden of proof lies on the complainant and the complaint has to be lodged within 2 years of the alleged date of sustaining damage. But too frequent allegation of negligence is further causing a strained relationship and mistrust between the doctor and his patient.

The term "Medical Ethics" as it is, deals with Ethical principles for the practice of Medicine and medical practice is based on the doctor patient relationship. In these principles the interest of the patient has been given priority whereas the interest of the doctor has been overlooked. In the present scenario abiding by the principles of medical ethics may lead to victimisation of violation of human rights. Autonomy of the doctor is at stake and inspite of the best efforts charges of medical negligence may be formed if the outcome is not satisfactory.

MODIFICATIONS OF ETHICAL PRINCIPLES

It is time we need to rethink and reframe the Medical Ethics to safeguard our interests. The principles should be at par with the changing trends of the modern society. The principles of "Dignity" and "Unity" should be incorporated along with the existing four pillars of Medical Ethics. "Dignity" refers to the duty of the doctors to uphold the dignity of the profession. Every medical practitioner has the obligation to secure the respect and esteem of the profession. Any intention to malign the reputation of the profession should be dealt appropriately. Service to the society should not be at the cost of ignominy to the profession. Self respect and respect for the medical community should be upheld by the doctors against all odds. Professionalism is the need of the hour. A therapeutic relationship should be built based on competent and compassionate care that fulfils the expectations of the patient.[6]

"Unity" among the members of the fraternity should be expressed in every sphere of life Fellow feelings and brotherhood should be an integral part of the medical community. United efforts must be taken to provide support to any medical professional in cases of violation of human rights against him. Such moral support would alleviate the stress of the practitioner in his professional career. The World Health Organisation has developed the surveillance systems of attacks on healthcare (SSA) to monitor such attacks on medical professionals in conflict zones.[8] Unfortunately no such system exists to monitor such attacks on practitioners in non conflict zones.

CONCLUSION

The human rights of the noble professional should be protected. If we fail to act in a positive manner and intent, days are not far when medical treatment would be only AI (artificial intelligence) dependent and there would be no need to protect the human rights of the noble man.

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Review Article

Diabetes mellitus, metabolic syndrome, and sleep disorders: An underestimated relationship

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Abstract

Diabetes mellitus (DM) is the most prevalent endocrine disorder globally. DM is under-evaluated and less efficiently managed in terms of ruling out comorbid conditions associated with it and predisposing factors resulting in poor outcomes. Sleep disorders are more common than usually diagnosed due to less awareness in the community regarding the importance of timely diagnosis and the impact of interventions related to proper sleep hygiene and sleep structure. Obstructive sleep apnea (OSA) is independently associated with cardiovascular and cardiometabolic risk in several large epidemiological studies. OSA leads to several physiological disturbances, such as intermittent hypoxia, sleep fragmentation, and an increase in autonomic tone. Metabolic syndrome (MS) is an adverse outcome that is typically associated with obesity. It is a cluster of metabolic risk factors for type 2 DM (T2DM) and cardiovascular diseases (CVDs), including central obesity, hypertension, hyperglycemia, insulin resistance, and dyslipidemia. T2DM is often associated with OSA, and a bidirectional relationship may exist between the two diseases, mediated by both weight- and physiology-dependent mechanisms. OSA is highly associated with T2DM, and treatment of OSA may have a positive impact on the cardiometabolic profile. In this review, we have attempted to summarize the impact of sleep disorders on MS and DM, and vice versa, with special emphasis on newer medical options in the management of DM and cardiometabolic syndrome.

Keywords: Diabetes mellitus, metabolic syndrome, OSA, sleep disorders, T2DM

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SALIENT FEATURES

1. Obstructive sleep apnea (OSA) is the risk factor for metabolic syndrome (MS), even in lean patients. Type 2 diabetes mellitus (T2DM) is very prevalent in OSA, and bidirectional relationship exists between these diseases.
2. Intermittent hypoxia, respiratory efforts, sleep fragmentation, and sympathetic activity related to nighttime obstructive respiratory events have been implicated in the dysregulation of glucose and lipid metabolism.
3. The impact of continuous positive airway pressure (CPAP) on MS and T2DM is difficult to isolate, but it seems to improve glucose metabolism and blood pressure.
4. Weight loss is the cornerstone of MS and T2DM treatment; however, recently developed drugs (GLP-1 receptor agonist and gliflozins) open the door of new perspectives, as these lead to significant cardiovascular risk reduction and reduce the likelihood of T2DM patients developing OSA.

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INTRODUCTION

Diabetes mellitus (DM) is characterized by chronic hyperglycemia arising from dysregulation of carbohydrate, lipid, and protein metabolism. Type 2 DM (T2DM) is the most common form of diabetes, accounting for 90% of cases, affecting over 460 million worldwide, with projections expecting this number to rise to over 700 million in just 25 years. The main cause of T2DM is insulin resistance in skeletal muscle, liver, and adipose tissue, eventually giving rise to pancreatic β cell dysfunction and failure. These impairments result in a chronic hyperglycemic state, which, if left untreated, can cause serious complications, including macrovascular and microvascular diseases. Mirroring this secular rise in T2DM, over the last century, there has been an inverse decline in sleep duration.[1,2]

Both the development and control of T2DM seem to be affected by sleep quality and duration. Many researchers suggest that optimizing sleep duration and quality should be tested as an intervention to improve glucose control in patients with T2DM. On the other hand, it should also be taken into account that poor glycemic control in T2DM and T1DM individuals may favor the development of sleep disorders.[3] In addition to diabetes, overweight and obesity have been growing in prevalence at an alarming rate.

Sleep is a complex behavioral and physiological process, divided into rapid eye movement (REM) sleep and non-REM sleep. Although generally viewed as a passive condition, it is a highly active and dynamic process. The later stages of non-REM sleep, stages 3 and 4, also known as slow-wave sleep, are most refreshing and restorative. Sleep is important not only for restoring brain functions but also for modulating a variety of metabolic, endocrine, and cardiovascular systems. Normally, during non-REM sleep, there is a decrease in metabolic rate, sympathetic nervous system (SNS) activity, blood pressure, and heart rate, and an increase in cardiac vagal activity. However, this sleep physiology is disrupted in persons with sleep disorders, including obstructive sleep apnea (OSA).[4]

In the third edition of the International Classification of Sleep Disorders (ICSD), five major categories of sleep-disordered breathing (SBD) were defined as follows:

1. Obstructive sleep apnea syndrome (OSAS)
2. Central sleep apnea (CSA) syndrome
3. Sleep-related alveolar hypoventilation
4. Sleep-related hypoxemia disorder
5. Isolated symptoms and normal variants

Apnea in adults is scored when there is a drop in the peak signal excursion by ≥ 90% of pre-event baseline using an oronasal thermal sensor (diagnostic study), positive airway pressure (PAP) device flow (titration study), or an alternative apnea sensor for ≥10 s. Hypopnea in adults is scored when the peak signal excursions drop by ≥30% of the pre-event baseline using nasal pressure (diagnostic study), PAP device flow (titration study), or an alternative sensor for ≥10 s in association with either ≥3% arterial oxygen desaturation or an arousal.[5] For adults, sleep hypoventilation is scored when the arterial PCO2 (or surrogate) is >55 mm Hg for ≥10 min, or there is an increase in the arterial PCO2 (or surrogate) ≥10 mm Hg (in comparison to an awake supine value) to a value exceeding 50 mm Hg for ≥10 min.[5]

OSA is frequently associated with comorbidities, including pulmonary, cardiovascular, metabolic, neoplastic, neuropsychiatric, or renal diseases. OSA is an independent risk factor for development, progression, and control of numerous cardiovascular and metabolic diseases, which represent the principal morbidity and mortality due to OSA.

Risk factors and conditions associated with OSA: Criteria for screening and suspecting sleep-disordered breathing

Risk factors at clinical examination are as follows:

1. Obesity, high body mass index (BMI)
2. Neck circumference of >43 cm in men and >38 cm in women
3. Male sex
4. Age >50 years
5. Postmenopausal state
6. Pregnancy/pregnancy-induced hypertension
7. Ethnicity (African–Americans, Asian populations)
8. Nasal obstruction
9. Craniofacial anatomical abnormalities (retrognathia, macroglossia, increased or modified Mallampati score, Friedman tongue position, high arched palate)
10. Neuropathy or myopathy of upper airway, that is, genioglossus muscle

Conditions associated with OSA:

1. Hypertension (particularly resistant), nondipping pattern
2. Atrial fibrillation
3. Stroke and transient ischemic attacks
4. Congestive heart failure (CHF)
5. Pulmonary hypertension (PH)
6. Obesity hypoventilation syndrome (OHS)
7. MS
8. T2DM
9. Polycystic ovarian syndrome

10. Acromegaly
11. Hypothyroidism
12. Chronic lung disease (Asthma, chronic pulmonary diseases, idiopathic pulmonary fibrosis)
13. End-stage kidney disease
14. Parkinson's disease
15. Down syndrome and Pierre Robin syndrome

Sleep and T2DM

In the past, T2DM was considered a disease of older age groups. Today, it is well established that even with a higher incidence in older people, T2DM may occur at any age. This change is attributed to the spread of a "Western modern society lifestyle," which includes higher food consumption, sedentary behavior, and shorter sleep duration. Epidemiological data have suggested higher risk of obesity and T2DM in individuals with shorter sleep duration (<5–6 h/night) as well as those with poor sleep quality. Studies have also reported higher risk of obesity and T2DM in individuals with long sleep duration (≥9 h/day).

The categories of sleep disturbances that contribute to obesity and T2DM include the following: (1) alterations of sleep duration, chronic sleep restriction, and excessive sleep; (2) alterations in sleep architecture; (3) sleep fragmentation; (4) circadian rhythm disorders and disruption (i.e., shift work); and (5) OSA.[6] A recent systematic review and meta-analysis demonstrated sleep disturbances as significant risk factors for diabetes with effect sizes similar to those imparted by traditional risk factors. Difficulty initiating sleep increased the risk of T2DM by 55%, while difficulty maintaining sleep increased its risk by 74%. Similarly, the risk of developing T2DM associated with insufficient (≤5 h/day) or excessive sleep duration (≥9 h/day) or performing shift work was comparable to that of being physically inactive.[7]

OSA, obesity, and sleep duration

OSA, a chronic condition characterized by frequent airflow cessation caused by episodes of upper airway collapse during sleep, is the most common type of sleep-disordered breathing (SDB).[8] As several authors have clearly established, obesity is probably the most important risk factor for OSA.[9] According to Pillar and Shehadeh,[9] some 60%–90% of adults with OSA are overweight, and the relative risk of OSA in obese subjects (BMI > 29 kg/m^2) may be as great as 10 times or more. In a longitudinal study with 690 subjects, Peppard *et al.*[10] reported that a 10% weight gain predicted an approximate 32% increase in the apnea–hypopnea index (AHI), a 10% weight loss predicted a 26% decrease in the AHI, and a 10% increase in weight predicted a sixfold increase in the odds of developing moderate-to-severe SDB.

The reason for the high prevalence of OSA among obese subjects, particularly in cases of greater central adiposity, is the distribution of fatty tissue that can lead to anatomical and physiological changes. The most important alterations seem to be a reduction in pharyngeal lumen size due to fatty tissue within the airway or on its walls, which increases pharyngeal collapsibility; a decrease of upper airway muscle protective force due to fatty deposits in the muscle; and a reduction of upper airway size secondary to the mass effect of the large abdomen on the chest wall and tracheal traction.[10]

Conversely, OSA may predispose individuals to gain weight, in part because of its association with sleep deprivation, daytime sleepiness, and disrupted metabolism. These seem to be related to changes in sympathetic tone, hormone regulation, and behavior. Behavioral changes consist of more waking time and daytime sleepiness, more time spent eating, and fatigue.[9] Pathways explaining the vicious cycle of T2DM and sleep are illustrated in Figure 1.[8]

OSA and T2DM

Subjects with OSA are 9.1 times more likely to present metabolic syndrome (MS) than those without OSA. MS is a complex syndrome linked to central obesity that confers increased risk for T2DM. Aside from the contribution of obesity, SDB/OSA has been shown to be independently associated with other neuroendocrine–metabolic changes that might favor the development of T2DM. Reinforcing this point, SDB/OSA is known to affect glucose metabolism, insulin sensitivity, pancreatic β

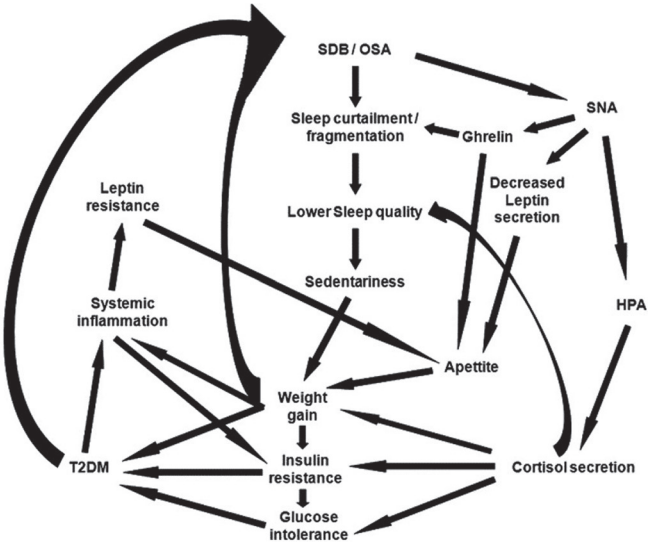

Figure 1: Pathways composing the vicious circle of T2DM and sleep

cell function, and night sleep quality, resulting in daytime fatigue and sleepiness, which might favor physical inactivity, thus predisposing sufferers, directly and indirectly, to the development of obesity and T2DM.[11-13]

Punjabi and Beamer[13] have shown that subjects with mild, moderate, and severe SDB, compared to normal subjects (AHI < 5 events/h), displayed a 26.7%, 36.5%, and 43.7% reduction in insulin sensitivity, respectively. In individuals with T2DM, who were shown to present a high prevalence of OSA, the more severe the OSA, the poorer the glycemic control is.[14]

Interestingly, in this association, OSA does not only increase the risk for T2DM, but it also seems to be affected by this endocrine–metabolic disease.[15] Studying 941 men, West *et al.*[15] concluded that T2DM may be a significant independent contributor to the risk of OSA. Their analysis suggests that 23% of the T2DM population presents OSA. After correction for BMI, which explained 13% of the variance in OSA, diabetes explained a further 8%.[15]

Other sleep disorders and T2DM

Difficulties in initiating and/or maintaining sleep increase, by two- to threefold, the risk of later onset of T2DM. This association is independent of known risk factors for diabetes and is not attributable to treatments for sleep disorders.[16] Thus, besides obesity and OSA itself, difficulties in maintaining sleep and short sleep duration due to sleep disorders or as a behavior imposed by modern lifestyle exert adverse effects on glucose metabolism, increasing the risk for obesity and T2DM or exacerbating metabolic control in T2DM subjects.[16]

On the other hand, Trento *et al.*[17] recently published a study showing a significantly higher sleep fragmentation index and increased movements during sleep in diabetic subjects, compared to a healthy control group. Their results suggest that T2DM is associated with sleep disruptions even in the absence of sleep disorders or obesity.

At this point, we may perceive a vicious circle involving T2DM, obesity, and sleep impairments, such as OSA and sleep loss. T2DM is strongly associated with abdominal obesity,[18] and both conditions are associated with OSA and other sleep disorders. Sleep impairments impact wakefulness, leading to fatigue and physical inactivity, and may increase hunger and the time available for eating, which favor weight gain. OSA, as well as perceived sleep debt, may impair glycemic control in subjects with T2DM because these factors decrease glucose tolerance and increase insulin resistance. For this reason, treating OSA can improve metabolic control in subjects with T2DM.[18] Tasali *et al.*[19] documented that OSA may represent a novel risk factor for MS and diabetes, and thus, clinicians should be encouraged to systematically evaluate the presence of metabolic abnormalities in OSA and vice versa. Tasali *et al.*[19] have reported plausible mechanisms for concurrent occurrence and sharing of common risk factors as shown in Figure 2.[19]

Physiological pathways: Sympathetic contribution

Activation of the SNS is one of the best-understood consequences of stressful situations, such as OSA and other sleep impairments, including sleep curtailment. Sympathetic activation during OSA is partially caused by the resulting hypoxemia and hypercapnia, which act through chemoreceptor reflexes and other mechanisms. In individuals with OSA, these sympathetic-drive changes persist during daytime wakefulness, apparently due to hypoxia. Although hypercapnia, as hypoxia, leads to SNS activation, it does not promote a lasting effect.[20]

Among the pathways through which SNS activation is likely to predispose to obesity, glucose impairment, MS, and T2DM, the two most well-known are the inhibition of leptin secretion and the stimulation of the hypothalamic–pituitary–adrenal (HPA) axis, resulting in excessive cortisol secretion, which impairs glucose homeostasis.[21]

Physiological pathways: HPA axis contribution

As mentioned above and in Figure 2, SNS, activated by sleep impairment, stimulates the HPA axis. Cortisol, a glucocorticoid secreted as a result of HPA activity, has effects throughout the body, some of them tightly correlated to metabolism in peripheral tissues. Exposure to excessive glucocorticoid levels leads to insulin resistance, weight gain, and MS, by increasing glucose output and lipogenesis, decreasing glucose utilization, and inhibiting lipid mobilization in the presence of insulin, especially from the visceral adipose tissue.[22] Although cortisol levels do not seem to be altered after 24 h without sleep, Leproult *et al.*[23] found changes in cortisol levels in the evening following the night of sleep deprivation. After total or partial sleep deprivation, plasma cortisol levels were higher on day 2 than on day 1 (37% and 45% increases, $P = 0.03$ and 0.003, respectively), and the onset of cortisol secretion was delayed by at least 1 h.[23] In another study, glucose tolerance was lower in the sleep-debt condition than in the fully rested condition ($P < 0.02$), in parallel with increased evening cortisol concentration ($P = 0.0001$) and activation of the SNS ($P < 0.02$).[22] In addition to sleep deprivation, OSA, as expected, was also found to be associated with increased

levels of both cortisol and catecholamines. Figure 3 shows pathophysiological pathway contributing to decreased insulin sensitivity.[24]

It is, therefore, possible to conclude that sleep disorders affect both the SNS and the HPA axis, negatively impacting carbohydrate metabolism and favoring the development of glucose intolerance, which might lead to T2DM. On the other hand, it is interesting to note that HPA hyperactivity is a known cause of sleep impairments, such as insomnia, sleep fragmentation, and shortened sleep time.[24]

Physiological pathways: Appetite regulation contribution

As recently revealed, sleep disorders impact the regulation of appetite, leading to decreased satiety and increased caloric intake, which strongly contributes to the development of obesity. Importantly, obesity is one of the main components

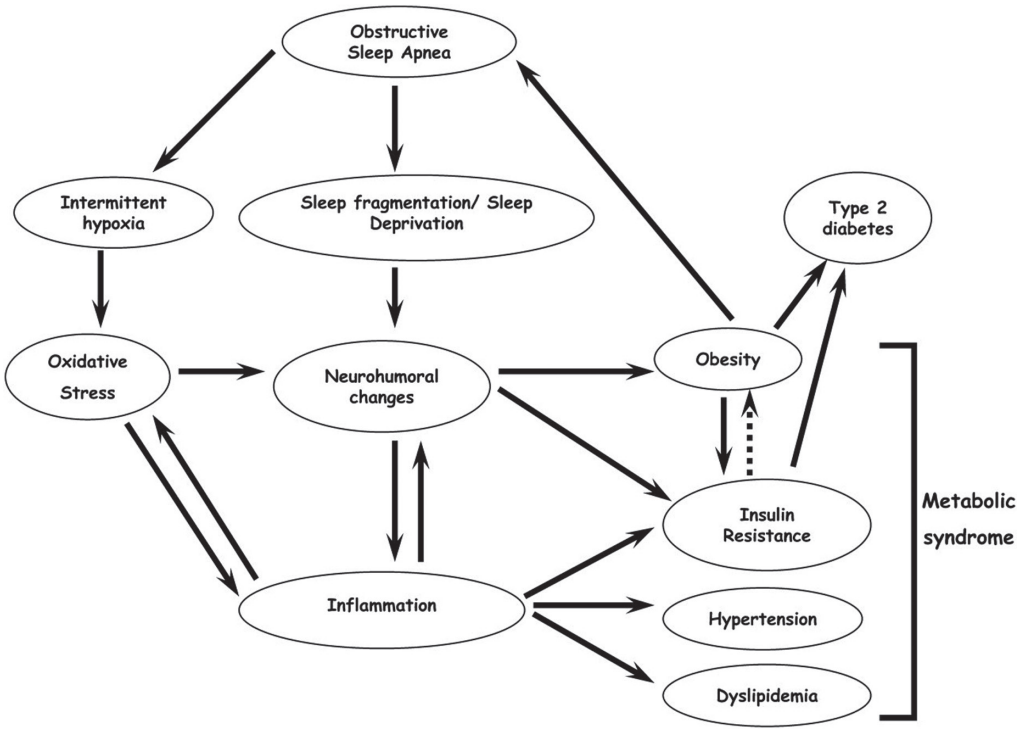

Figure 2: Possible mechanistic links between obstructive sleep apnea, metabolic syndrome, and type 2 diabetes

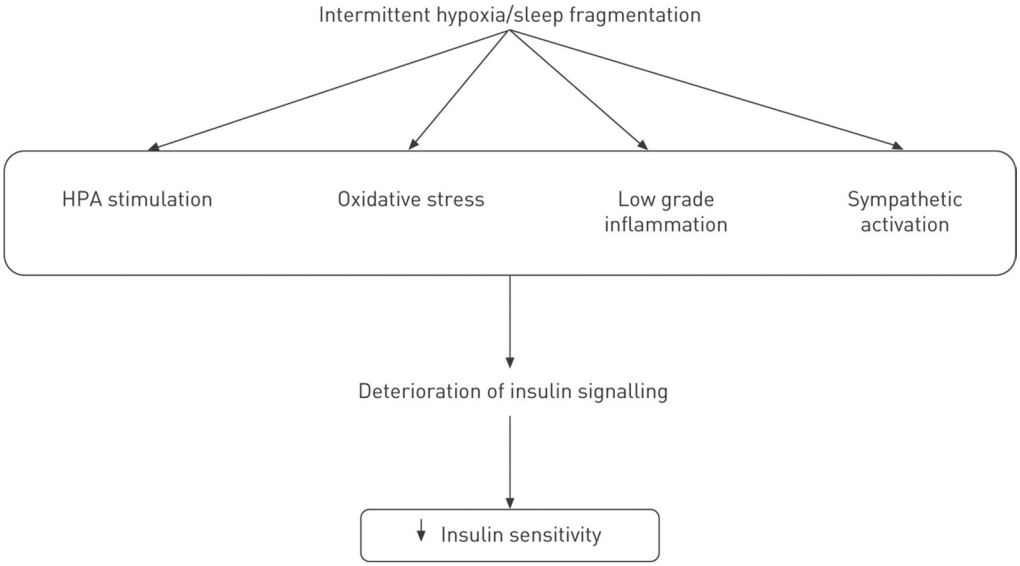

Figure 3: Intermediary mechanisms implicated in the deterioration of insulin sensitivity in obstructive sleep apnea patients

of MS and is a step toward T2DM and OSA. Although we are aware that there are several hormones and neuropeptides involved in appetite regulation, such as cholecystokinin, glucagon-like peptide-1 (GLP-1), and peptide YY3-36, among others, we will focus here on some hormones already established to be affected by sleep impairment: leptin, insulin, and ghrelin.

Leptin is primarily produced by adipocytes, and its level in the blood is proportional to fat mass, insulin is secreted by pancreatic β cells acutely in response to food intake. These hormones convey anorexigenic information to the hypothalamus, suppressing appetite and affecting energy expenditure. That is the reason why leptin-deficient children exhibit voracious feeding behavior and develop extreme obesity, an effect also found in mice. Although administration of exogenous leptin to both organisms results in a remarkable decrease in energy intake and fat mass, the administration of exogenous leptin fails to reduce adiposity in most cases of human obesity. The reason for this is a state of leptin resistance, which explains the high circulating leptin levels observed.[25]

In contrast with the hunger- and appetite-suppressing signals of leptin and insulin, ghrelin conveys an appetite-stimulating message to the hypothalamus. Ghrelin is primarily secreted by the stomach and rapidly suppressed by food intake. As discussed above, OSA and obesity are associated with high levels of leptin, several studies have found that short sleep duration is associated with decreased levels of leptin and increased levels of ghrelin.[26] Spiegel *et al.*[27] reported that a 2-day sleep restriction is associated with an 18% reduction in circulating leptin and a 28% elevation in ghrelin, concomitant with an increase in appetite. Although Nedeltcheva *et al.*[28] found no significant differences in serum leptin and ghrelin after sleep restriction, as did Spiegel *et al.*, they did report increased appetite for high-calorie and high-carbohydrate foods in the sleep-deprived subjects. Since the subjects studied by Nedeltcheva *et al.*[28] were overweight, and for this reason, predisposed to OSA, their leptin levels were higher and did not decrease, probably as a consequence of leptin resistance.

In a study of sleep restriction, Spiegel *et al.*[27] concluded that sleep modulates the neuroendocrine control of appetite, reporting a decrease in mean and maximal levels as well as in the rhythm amplitude of leptin (−19%, −26%, and −20%, respectively), concomitant with SNS activation, during sleep restriction compared with sleep extension. This finding may be at least partially explained by the stressful effect of sleep restriction that activates the SNS, which, in turn, inhibits plasma leptin secretion by adipocytes. Moreover, short sleepers present lower glycemia at the end of an oral glucose challenge, which contributes to weight gain by increasing hunger and food intake. Therefore, impairment of appetite regulation might be a consequence of short sleep duration or be due to leptin and insulin resistance (the hallmarks of obesity and T2DM) and be exacerbated by OSA.

To explore in more detail the association between the sleep–wake cycle, appetite, and metabolism, it is necessary to consider the role of the neuropeptides called orexins or hypocretins. Orexin A and orexin B are excitatory neuropeptides found in the lateral hypothalamus and perifornical area. They are both stimulated by ghrelin, promote wakefulness, and increase appetite and SNS activity.[26] Moreover, besides the downregulation of satiety, the promotion of short sleep time, and the stimulation of the HPA axis by increased SNS activation, ghrelin promotes adipogenesis and decreases energy expenditure, fat catabolism, and lipolysis.[29] Therefore, this might be one of the main reasons why individuals with short sleep duration are prone to gain weight and increase the risk of developing OSA and T2DM.

Physiological pathways: Contributions of inflammatory processes

Obesity and T2DM are known to be associated with chronic systemic inflammation. Interestingly, in two experiments in which 10 healthy adult subjects stayed awake for 88 consecutive hours and another 10 subjects were assigned to sleep for either 8.2 h (control) or 4.2 h (partial sleep deprivation) for 10 consecutive days, the sleep-restricted subjects from both experiments presented increased blood concentrations of high-sensitivity C-reactive protein (CRP), a marker that reflects active systemic inflammation.[30] CRP was identified as one of the major serum leptin-interacting proteins, and it seems to be one of the main agents responsible for leptin resistance. According to Chen *et al.*,[31] human CRP directly inhibits the binding of leptin to its receptors and blocks its ability to signal in cultured cells.

In addition to sleep restriction, OSA is also associated with CRP and pro-inflammatory cytokines. In a study comparing subjects with OSA with a non-OSA matched control group, it was observed that CRP levels were significantly higher in OSA patients, and CRP levels were independently associated with OSA severity.[32] In another study, plasma interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) levels were elevated in patients with OSA but not in controls.

According to Kapsimalis *et al.*,[33] cytokines may either promote or inhibit sleep through their interactions with

different brain regions. Some of the sleep alterations that cytokines may induce could be mediated by changes in nitric oxide synthesis, effects on neurohormonal systems such as growth hormone releasing hormone, and activation of the HPA axis.[33] Therefore, since obesity, T2DM, sleep disorders, and sleep restriction are associated with increased inflammatory response, we can only come to the conclusion that the pro-inflammatory effects of one disorder influence the expression of, and aggravate, the other disorders.

Sleep and type 1 diabetes

The interactions between type 1 diabetes mellitus (T1DM) and sleep were revealed recently. The nongenetic factors that lead to the development of T1DM are not fully understood. Sleep disorders do not seem to trigger T1DM, as they seem to do for T2DM. Villa *et al.*[34] point to central apnea as one of the interactions, as it is more frequent and lasts longer in children with T1DM than in children without diabetes. In the same article, they report that apnea events during sleep correlate significantly with poor glycemic control and with the duration of diabetes. Furthermore, it has been shown that rapid changes in glucose levels experienced by T1DM individuals, independent of absolute glucose levels, may affect night sleep, resulting in awakening. Therefore, considering these and other evidence and the complaints of excessive daytime sleepiness and lower sleep quality among diabetics, we conclude that glycemic variation and poor glycemic control in T1DM patients affect the sleep–wake cycle.[35] Pathophysiological mechanisms involved in T1DM and sleep are explained in Figure 4.

Pillar *et al.*[36] have also observed in T1DM children a trend toward decreased total sleep time, increased sleep latency, and decreased sleep efficiency, along with an association between hypoglycemia during night sleep with an increase in sleep efficiency. Although it might seem contradictory that hypoglycemia during night sleep is associated with increased sleep efficiency while rapid glucose level changes result in awakening, this is possible because hypoglycemia does not always mean a rapid glucose level decrease. As Pillar *et al.*[36] have shown, when this decrease is fast, it leads to awakening, but when it is slow, T1DM children might continue sleeping, which is potentially dangerous.

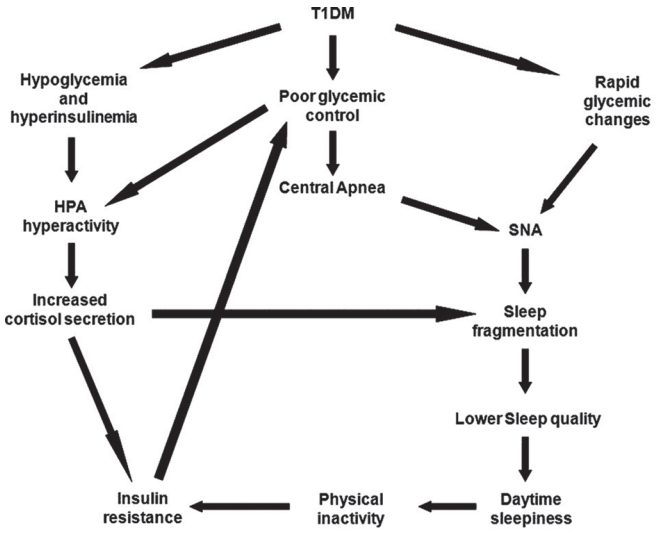

Figure 4: Pathways composing the vicious circle of T1DM and sleep

The physiological connection between exposure to acute or prolonged hypoglycemia and sleep disorders should be similar to that involved in sleep problems caused by OSA. As discussed before, OSA, as well as hypoglycemia, stimulates the SNS as a stress response, leading to stimulation of the HPA axis and cortisol secretion. The hyperinsulinemia in T1DM patients promotes HPA hyperactivity as well. Chan *et al.*[37] have also reported that poorly controlled or uncontrolled diabetes causes diurnal hypersecretion of glucocorticoids and altered regulation of the HPA axis. As already seen, HPA axis hyperactivity has consequences on sleep, impairing sleep quality by leading to sleep fragmentation, decreased slow-wave sleep, and shortened sleep duration. The pathway composing vicious cycle in T1DM and sleep has been shown in Figure 4.[8]

Jauch-Chara *et al.*[38] brought more evidence to this field, reporting higher blood levels of growth hormone, epinephrine, and adrenocorticotropic hormone throughout the night, as well as a tendency toward higher cortisol levels during the first half of the night, in T1DM patients compared with healthy control subjects. Interestingly, in the experiment, nocturnal hypoglycemia was prevented, indicating that the higher levels of counterregulatory hormones did not result from hypoglycemia, at least not during the experimental night. The authors suggest that the slightly but persistently elevated concentrations of glucose and insulin might be responsible for stimulating HPA activity and epinephrine release.[38]

Type 2 DM, MS, NASH, NAFLD, and OSA

There is a strong relationship between MS and OSA. A recent meta-analysis highlighted the fact that OSA and poor sleep quality are associated with an increased risk of DM, that is, the same magnitude of traditional risk factors for T2DM. OSA may adversely affect the course of T2DM complications such as retinopathy, kidney disease, or foot ulcers. A recent longitudinal study reported worse cardiovascular prognoses in patients with T2DM and incident OSA compared to patients who did not develop

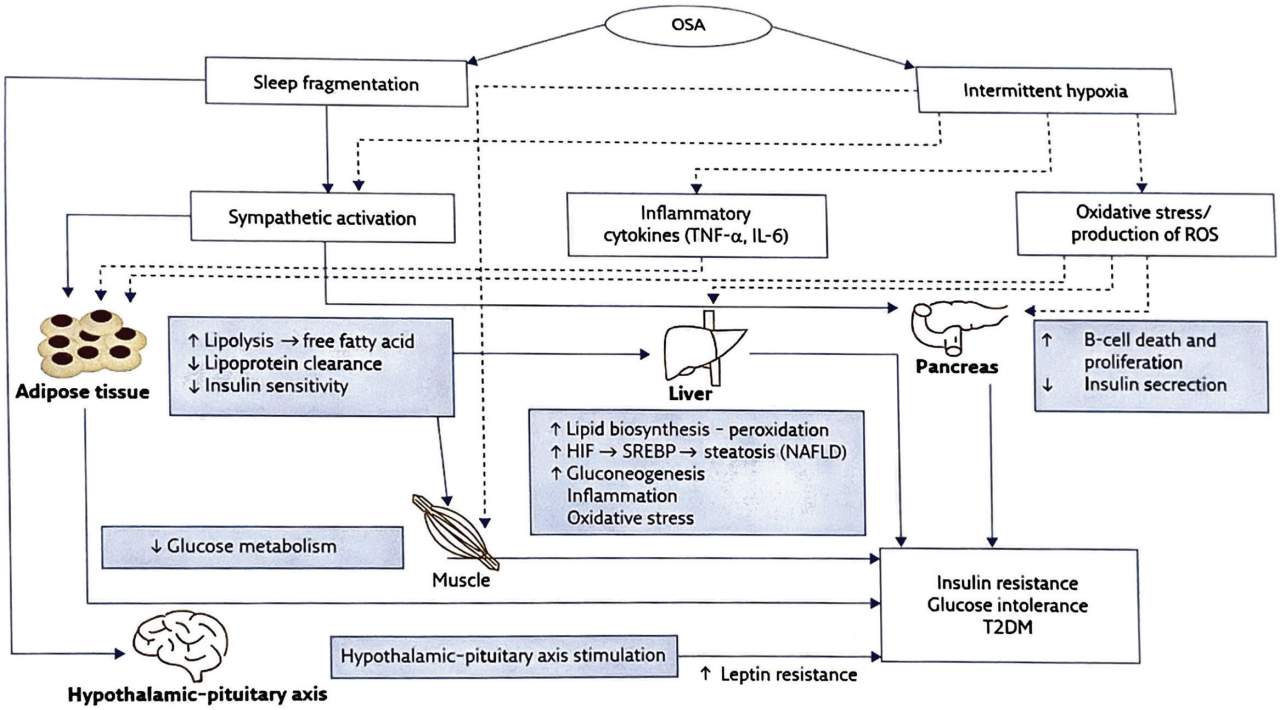

Figure 5: Showing pathophysiological dysregulations in OSA (TNF: tumor necrosis factor alfa, IL: interleukin, ROS: reactive oxygen species, HIF: hypoxia-inducible transcription factor, SREBP: sterol regulatory element-binding protein)

OSA during follow-up.[39,40] Possible pathophysiological mechanisms that may explain the increased risk of MS and T2DM in OSA, independently of obesity, include intermittent hypoxia, oxidative stress, cytokine secretion, and systemic inflammation, as shown in Figure 5.[40]

Oxidative stress can induce disturbances in glucose homeostasis, insulin resistance, and dyslipidemia. Intermittent hypoxia and sleep fragmentation provoke inflammatory cytokine secretion and provide a possible mechanism for development of MS. In this setting, impaired insulin action in peripheral tissues and increased insulin-resistant dyslipidemia and hypertension may occur. OSA and MS are thus synergistic CVD risk factors.[41,42]

In the European Sleep Apnea Database (ESADA) cohort,[43] a linear relationship between levels of total cholesterol, low-density lipoprotein, triglycerides, and low levels of high-density lipoprotein and the severity of OSA (reflected by AHI or oxygen saturation index) was observed. In particular, lipid levels were higher in OSA patients with central obesity. There is a growing body of evidence that OSA is associated with nonalcoholic fatty liver disease (NAFLD), especially in obese patients. Insulin resistance, T2DM, obesity, and intermittent hypoxia are contributors to liver dysfunction in OSA, ranging from steatosis (nonalcoholic steatohepatitis [NASH]) to liver cirrhosis and hepatocarcinoma. A very high prevalence of NAFLD (64%–91%), a much higher than in general population (25%–40%), has been documented in OSA patients. The association between NAFLD and OSA persists in the absence of obesity. Furthermore, NAFLD severity increases with OSA severity.[44,45]

Glycemic control in diabetic patients, assessed by glycosylated hemoglobin (HBA1c) level, is adversely affected by OSA. In the ESADA cohort, increasing AHI in patients with T2DM was associated with a linear increase in HbA1c. Poor glycemic control correlated with the frequency of respiratory events occurring in REM sleep but not in non-REM sleep, suggesting role of OSA-associated sympathetic activation in its pathogenesis. Recent studies using continuous glucose monitoring have reported worse diurnal and nocturnal glucose profiles in diabetic patients with moderate-to-severe OSA compared to patients with mild OSA.[43-46]

Treatment options

Lifestyle modifications, including exercise and dietary changes (e.g., Mediterranean diet), are recommended to achieve weight loss and increased insulin sensitivity, with the goal of preventing the progression of the components of MS.[47]

In obese patients, weight loss of 5%–10% leads to decrease in blood pressure (BP), a better lipid profile, improved

insulin sensitivity, and a reduction in inflammatory markers, ameliorating the risk of coronary heart disease.[48]

In the xenical in the prevention of diabetes in obese subjects (XENDOS) randomized control trial (RCT), which included 3305 obese patients, orlistat treatment resulted in weight loss of 2.4% after 4 years and was also effective in decreasing the risk of T2DM, lowering BP, and improving insulin sensitivity and lipid profiles, as it acts by decreasing the absorption of intestinal fat.[49]

Role of the CPAP therapy

The impact of CPAP therapy on glucose metabolism remains unclear. A meta-analysis including 443 participants with MS (duration of CPAP intervention >2 weeks) showed a significant improvement in insulin resistance, measured by homeostatic model assessment index, but fasting glucose levels remained unchanged. Similar observations have been reported for lipid metabolism: it is unclear whether CPAP treatment can improve dyslipidemia and reduce cardiovascular risk in patients with OSA.[50]

In patients with T2DM and OSA, a recent meta-analysis of RCTs showed that the CPAP treatment decreased the HbA1c, fasting glucose, insulin resistance, and systolic blood pressure and diastolic blood pressure , but previous similar meta-analysis was negative. Such different results may derive from differences in sample size or from the poor sensitivity of HbA1c measurements to day–night changes compared to continuous glucose monitoring over 24 h, which has shown improved glycemic profiles during CPAP treatment. CPAP use for 4 h per night may be insufficient to affect glycemic control, whereas studies assessing the effects of CPAP treatment for 8 h per night showed significant metabolic improvements and decreased sympathetic activity in patients with prediabetes or T2DM after just 1 or 2 weeks of treatment.

Another study focused on patients with obesity and moderate-to-severe OSA who were randomly assigned to CPAP treatment, weight loss, or CPAP plus weight loss interventions for 24 weeks. Triglyceride levels were significantly reduced in the weight loss and combined intervention groups but not in the CPAP alone group. Therefore, CPAP alone does not appear to be sufficient to improve metabolic changes in obese OSA patients.[51]

In the ESADA cohort, the long-term effects of CPAP therapy on lipid profile were analyzed. After adjustment for age, sex, lipid-lowering medications, change in weight, CPAP compliance, and duration, only total cholesterol levels decreased significantly during follow-up, and duration of CPAP therapy was the only independent predictor for cholesterol reduction.[52]

As for other metabolic disturbances in OSA, the effect of CPAP on NAFLD is controversial. In the majority of recent studies, no impact of CPAP alone was observed.

Isolating the role of CPAP on dysmetabolic aspects of OSA remains challenging, as many confounders can influence MS: CPAP adherence, CPAP duration, glycemic control, the use and duration of antidiabetic and lipid-lowering drugs, sedentarity, obesity, physical activity, and diet.

New drugs

Several drugs are currently used to delay the occurrence of T2DM, with interesting recent developments. Metformin is associated with reduction in body weight, waist circumference, fasting plasma glucose, and triglycerides and has been shown to provide a 31% risk reduction in developing T2DM at 3 years.[50]

GLP-1 receptor agonists are a recently developed antidiabetic drug class, including albiglutide, liraglutide, lixisenatide, exenatide, semaglutide, and dulaglutide, administered subcutaneously or orally.[52,53] These drugs mimic the effects of incretins in the body and seem to be safe and well tolerated. In a recent review that included 56,004 patients, a cardiovascular mortality reduction of 12% in T2DM was achieved. In addition to improving glycemic control, reductions in weight loss, BP, and total cholesterol were also observed. More recently, interesting data have been published on the cardiovascular impact of liraglutide in MS. Although the exact mechanisms of action are still unknown, it seems that this molecule achieves direct anti-atherosclerotic action by decreasing plaque formation and progression. Similar to metformin, liraglutide treatment is associated with reductions in body weight and waist circumference in MS. Moreover, liraglutide, semaglutide, and dulaglutide are effective in reducing fat liver content and achieving resolution of NASH in up to 42% of patients.[52,53] The ROMANCE RCT on the effects of liraglutide alone or combined with CPAP in diabetic OSA patients is ongoing.[54]

Sodium–glucose cotransporter 2 (SGLT2) inhibitors (Gliflozins) are novel therapeutic agents for T2DM that inhibit glucose reabsorption in renal proximal tubules. These drugs also improve glycemic control and reduced body weight and BP, achieving the goal of decreasing cardiovascular events in MS. SGLT2 inhibitors appear to exert protective effects toward cardiovascular and respiratory diseases, including OSA. A recent study showed

that the combination of metformin and dapagliflozin led to the resolution of MS in 77% of patients and was more effective than monotherapy.[55] Another RCT found that empagliflozin reduced cardiovascular events in both OSA and non-OSA DM patients and reduced the incidence of OSA during follow-up, possibly in association with body weight reduction. Other smaller studies have reported similar effects, but it is still unclear whether SGLT2 inhibitors may exert additional protective effects in OSA patients.[56]

Learning points

1. MA, T2DM, and OSA are closely linked. OSA exerts a negative influence on metabolic functions through several pathophysiological mechanisms, including intermittent hypoxia, respiratory efforts, sleep fragmentation, and sympathetic activity.
2. OSA, short sleep duration, and obesity are strongly associated with each other, and each may aggravate or favor the development of the other. While in the past, the prevailing belief was that the conditions of OSA and T2DM were linked to obesity, recent findings reported above foster the interpretation that they may also be independently associated. Therefore, the incidence of one is higher when the other is present, and both are aggravated when in association with obesity.
3. Although the role of CPAP in the metabolic dysfunction associated with OSA is not well established, a recent meta-analysis showed a positive effect of CPAP for decreasing HBA1C, fasting blood glucose, insulin resistance, and systolic and diastolic blood pressure.
4. Beyond weight loss and metformin, new drugs such as GLP-1 receptor agonists and gliflozins have shown significant improvement in glycemic control and reduction in body weight and blood pressure.
5. These treatments can resolve NASH in a significant proportion of patients and also appear to exert protective effects toward the occurrence of cardiovascular and respiratory diseases, including OSA in T2DM patients.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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Original Article

A cross-sectional study of sleep quality in urban and rural adolescents with reference to their digital exposure

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Abstract

Background: With the widespread use of digital devices and increased screen time among adolescents, concerns have arisen regarding its potential impact on sleep quality. This study aims to investigate the correlation between excessive screen time and Pittsburgh Sleep Quality Index (PSQI) global scores in adolescents.

Materials and Methods: A cross-sectional study was conducted among 167 adolescents aged 10–19 years residing in rural and urban areas. Participants completed self-report questionnaires evaluating their screen time habits and sleep quality using the PSQI. Excessive screen time was defined as more than 2 h per day of exposure to digital screens, and an abnormal PSQI global score was defined as more than 5. Statistical analyses, including unpaired *t* test, Spearman's correlation, and chi-square test, were employed to examine the association between excessive screen time and PSQI global scores.

Results: The results revealed a significant positive correlation between excessive screen time and abnormal PSQI scores in adolescents ($r = 0.623$, $P < 0.001$). Adolescents reporting excessive screen time were significantly more prone to abnormal PSQI scores compared to those with lower screen time ($P < 0.0001$, $t = 9.63$, degree of freedom = 165).

Conclusion: This study highlights a correlation between excessive screen time and abnormal sleep quality in adolescents, as assessed by the PSQI. These findings underscore the importance of promoting healthy screen time habits among adolescents to mitigate potential adverse effects on their sleep quality and overall health. Further research is needed to explore the mechanisms underlying this relationship and to develop effective interventions to address this issue.

Keywords: Adolescents, cross-sectional study, digital devices, excessive screen time, Pittsburgh Sleep Quality Index, screen time habits, sleep quality

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INTRODUCTION

The equilibrium between the internal and external synchronizers is influenced by changes in daily habits. The changes in nightly habits and sleep hygiene have the potential to influence the sound physiological phenomena in human beings. While excessive screen time behaviors

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and insufficient sleep among adolescents have been extensively studied, few investigations have explored their association using a large nationally representative sample.[1] This study aims to investigate the correlation between excessive screen time and Pittsburgh Sleep Quality Index (PSQI) scores in adolescents. These components include the following:

- **Subjective sleep quality**: Participants rate their overall sleep quality on a scale from 0 (very good) to 3 (very bad).
- **Sleep latency**: This component assesses the time it takes for individuals to fall asleep after going to bed.
- **Sleep duration**: Participants report the number of hours they sleep per night.
- **Habitual sleep efficiency**: This component calculates the ratio of actual sleep duration to the total time spent in bed.
- **Sleep disturbances**: Participants rate the frequency of various sleep disturbances such as waking up in the middle of the night or having difficulty breathing during sleep.
- **Use of sleep medications**: This section asks about the use of sleep medications and their frequency.
- **Daytime dysfunction**: Participants rate the extent to which sleep problems interfere with their daily functioning.

The overall PSQI score is obtained by summing the component scores, resulting in a total score ranging from 0 to 21, with scores greater than 5 indicating poorer sleep quality. The Coronavirus disease of 2019 pandemic has led to increased screen time and changes in sleep habits among early adolescents. This pandemic was a triggering factor for the sudden changes in screen time habits and unhealthy sleep habits. Additionally, sedentary screen time has been found to negatively affect sleep quality in adolescents, particularly those with higher levels of anxiety.

There is evidence indicating that the use of digital screens by adolescents has been associated with poorer sleep quality, characterized by night awakenings, long sleep latency, and daytime sleepiness.[2] Some studies have investigated excessive screen time in adolescents. Excessive screen time in adolescents is correlated with poor sleep quality, as measured by the PSQI.[3,4] The studies found that increased screen time on various electronic devices, such as smartphones, computers, and video games, was associated with higher PSQI scores and a higher likelihood of reporting psychosomatic complaints.[5-7]

Specifically, screen time linked to smartphone usage on weekends and increased screen time while in bed were significantly associated with poor sleep quality. Additionally, exposure to screen time, particularly video games and computers, had a negative impact on sleep quality, particularly among adolescents at a higher risk of anxiety. These findings suggest that excessive screen time can have detrimental effects on sleep quality in adolescents, highlighting the importance of educational policies and interventions aimed at managing screen time and promoting healthy sleep habits.

Sleep physiology involves complex processes involving cycles of non-rapid eye movement (NREM) and rapid eye movement (REM) sleep, crucial for memory consolidation, hormone regulation, and overall health.[8] During NREM, the body repairs tissues and releases growth hormones, while REM supports cognitive function and emotional regulation.[9] Disruptions to these cycles can lead to sleep disorders, affecting both physical and mental well-being.[10] Prioritizing sleep hygiene and maintaining a consistent sleep schedule are essential for optimizing sleep physiology and overall health.[11]

Excessive screen time can negatively affect sleep physiology by affecting blue light exposure, disrupting the circadian rhythm, increasing mental stimulation, reducing sleep duration, and causing sleep fragmentation. Blue light suppresses melatonin, a hormone responsible for sleep–wake cycles, and can delay sleep onset. Additionally, late-night screen use can prolong awake time, leading to shorter sleep duration and sleep deprivation. Research suggests that screen time close to bedtime is associated with more frequent awakenings and less restorative sleep. Establishing healthy screen habits can improve sleep quality and overall well-being.[12]

Objectives

This study aims to determine the correlation between PSQI scores and excessive screen time among adolescents in rural and urban areas.

Methodology

A cross-sectional study was conducted among a sample of 167 adolescents aged 10–19 years. Participants completed self-report questionnaires assessing their screen time habits and sleep quality using the PSQI over 6 months (September 2022 to March 2023). This study was approved by the Institutional Ethics Committee (reference no. 799/U/IEC/ESICMC/S0184/09/2022). The data were collected after taking informed consent and assent forms from the participants and their guardians, respectively.

a. *Study design*: Observational, analytical, and cross-sectional
b. *Study population*: Adolescents (10–19 years; both males and females)

c. *Study site:* Rural Health Training Centre (RHTC), Ramachandrapuram, Hyderabad, Telangana, India, and Urban Health Training Centre (UHTC), Sanathnagar, Hyderabad, Telangana, India, attached to tertiary health care center.

Sample size calculation: Considering the prevalence of smartphone usage in Indian adolescents studied by Davey and Davey,[13] the sample size was calculated using the following formula:

$$N = (4PQ / d2)$$

where $P = 40\%$, $Q = (1 - P) = 60\%$, two-tailed alpha error = 5%, and power = 80%.

The sample size has been calculated as 150, assuming an absolute precision of 8%. Adjusting for a non-response rate of approximately 10%, the required sample size for the study would be 167 adolescent females.

Description of the sample:

- The World Health Organization defines adolescence as being between the ages of 10 and 19 years.[14]
- Screen time refers to the total time the study subjects spend with digital devices. Excessive screen time is defined as more than 2 h per day of exposure to digital screens.[15]
- Abnormal global PSQI scores are defined as scores exceeding 5.[16]

The study group consisted of the following:

1. *Cases (n = 89)*: Adolescents with screen time greater than 2 h per day.
2. *Controls (n = 78)*: Adolescents with screen time less than 2 h per day.

Inclusion criteria

The participants included in the study are adolescents aged 10–19 years attending the outpatient department of RHTC and UHTC who use digital devices.

Exclusion criteria

Adolescents unwilling to participate in the study and those who were not accompanied by a guardian were excluded. Cases and control subjects were excluded if they had any other diagnosed major medical conditions that could interfere with sleep patterns or if they had known central nervous system diseases such as seizure disorder, cerebrovascular disease, or dementia. The participants with daytime sleeping were also excluded from the study.

The PSQI was used. The self-report questionnaire assesses sleep quality among the participants. The PSQI consists of several components and questions that evaluate different aspects of sleep. The overall PSQI score is determined by summing the component scores, resulting in a total score ranging from 0 to 21. Scores more than 5 indicate poorer sleep quality. The PSQI assesses an individual's sleep quality and disturbances, with higher scores indicating worse sleep quality.

Statistical methods

After obtaining consent from guardians and the ascent of the participants (adolescents), data collection was performed using a predesigned semi-structured questionnaire (prepared in Google Forms). An Excel sheet was generated and further analysis was done. Statistical analysis was performed by using GraphPad (GraphPad Prism version 7 for Windows, GraphPad Software, La Jolla California USA) (Prism 7) with Spearman's correlation to examine the correlation between excessive screen time and PSQI global scores. ($P < 0.05$, statistically significant). Distribution frequency was observed in the descriptive analysis. Chi-squared test was used (χ^2) in the inferential analysis to analyze the association between screen time and PSQI Score in adolescents at 95% confidence intervals. The dependent variable was taken as the PSQI score, while the independent variable was screen time. A P value less than 0.05 was considered statistically significant.

RESULTS

Table 1 shows the demographic and socioeconomic profile of the participants.

From Figure 1, the frequency distribution of screen time exposure details reveals that the maximum mode of exposure is through mobile devices, followed by television, with the least exposure through laptops.

Table 1: Sociodemographic profile of study subjects

Sociodemographic profile	Categories	Number	Percentage (%)
Age (years)	10–14	78	46.7
	15–19	89	53.3
Sex	Male	79	47
	Female	88	52.7
Place of residence	Rural area	99	59.2
	Urban area	68	40.7
School type	Private	68	41.1
	Government	98	58.8
Socioeconomic class	Class I	35	21.1
	Class II	49	29.4
	Class III	52	31.7
	Class IV	29	17.6
Education	Primary	51	31.1
	Secondary	66	40.0
	Undergraduate	44	26.4

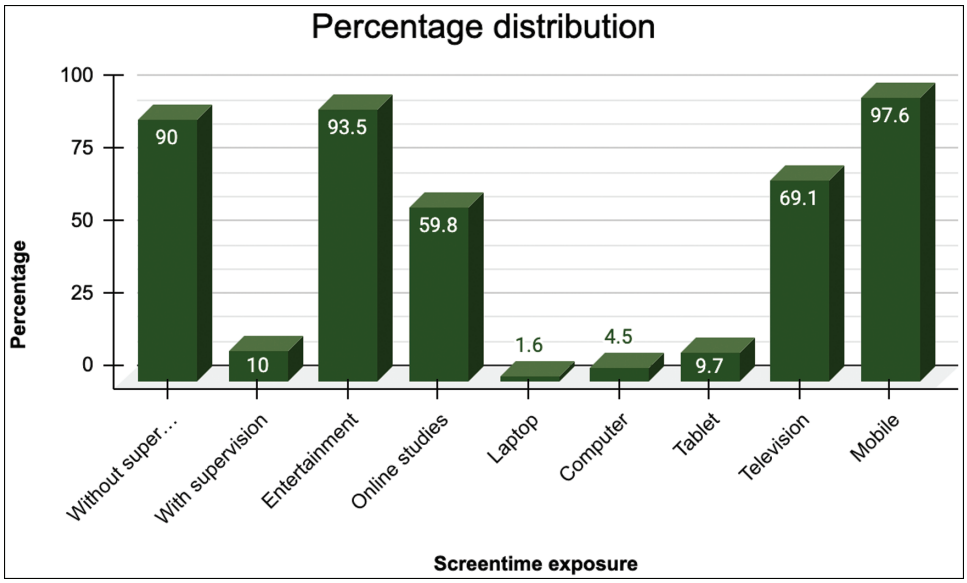
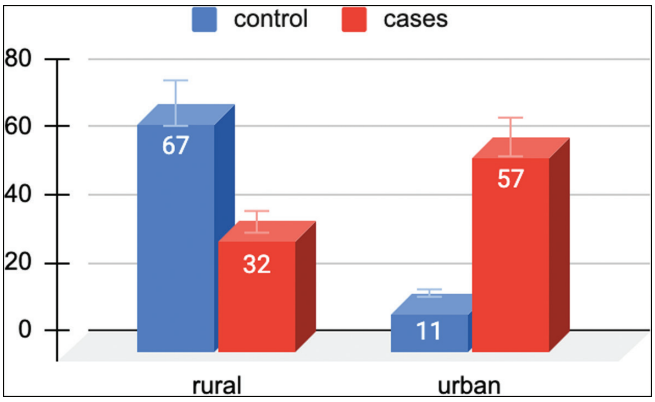


Figure 1: Frequency distribution of details of screen time exposure among cases and controls is given in Table 2

Regarding the purpose of screen time, it was found that 93.5% of participants used digital devices for entertainment, while 59.8% used them for online studies. Additionally, 90% of participants reported using the device without any supervision, while 10% reported using the device under supervision.

In Figure 2, the frequency distribution of participants based on age and gender showed that 53.3% of the participants were aged 15–19 years, while 46.7% of the participants were aged 10–14 years. The study included 52.7% of female participants and 47.3% of participants were male.



It can be observed that 51.9% of participants from rural areas were female, while 49.1% were male. In urban areas, 52.2% were female and 48.8% were male. For the rural participants, the percentages for socioeconomic classes I, II, III, and IV were 35.4%, 34.5%, 17.5%, and 12.6%, respectively. For the rural participants, the percentages of socioeconomic classes I, II, III, and IV were 18.2%, 11.8%, 39.9%, and 30.1%, respectively. Among the participants, 67.67% of controls and 32.32% of cases resided in rural areas, while 16.17% of controls and 83.82% of cases resided in urban areas. The odds ratio was calculated to be 10.84 at a 95% confidence interval with a z value of 6.06. The P value was less than 0.001, indicating statistical significance. Therefore, a significant association was found between the area of residence and screen time exposure, suggesting that the urban population has higher exposure to screen time compared to the rural population.

Table 2: The details of screen time exposure in study subjects

Modes and Media	Screen time exposure	Number	Percentage (%)
Device used	Mobile	161	97.6
	Television	114	69.1
	Tablet	16	09.7
	Computer	09	04.5
	Laptop	04	01.6
Purpose	Online studies	93	59.8
	Entertainment	157	93.5
Supervision	Yes	17	10
	No	153	90

Figure 3 indicates the frequency distribution of the PSQI global score among cases and controls. The frequency distribution of controls and cases indicates a higher PSQI global score in cases compared to controls. Hence, it can be interpreted that the participants with increased screen time are more likely to have a high PSQI global score.

Table 3 and Figure 4 show the mean and standard deviation among cases and controls. Considering the screen time, the mean hours of screen time in cases is 31.44, compared to 8.64 in controls. Considering the PSQI global score, the mean score in cases is 8.64, whereas it is 3.2 in controls [Table 3].

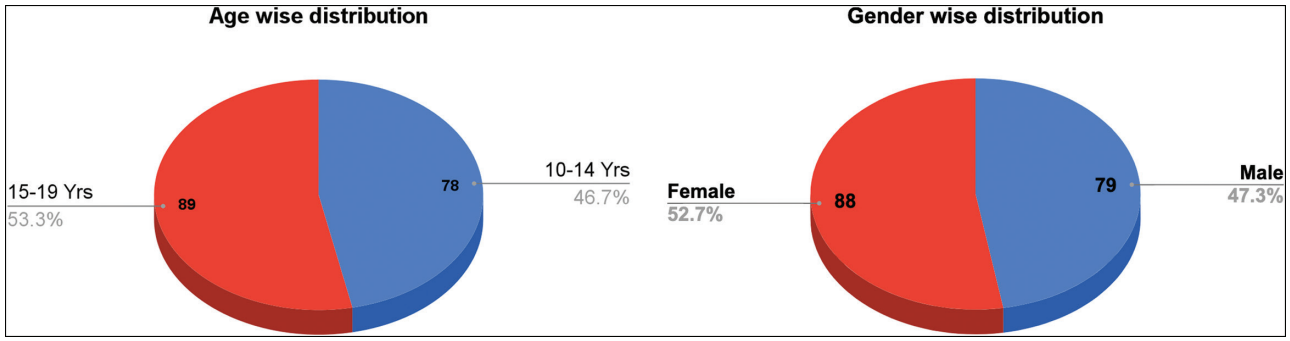


Figure 2: Frequency distribution of age and gender among cases and controls

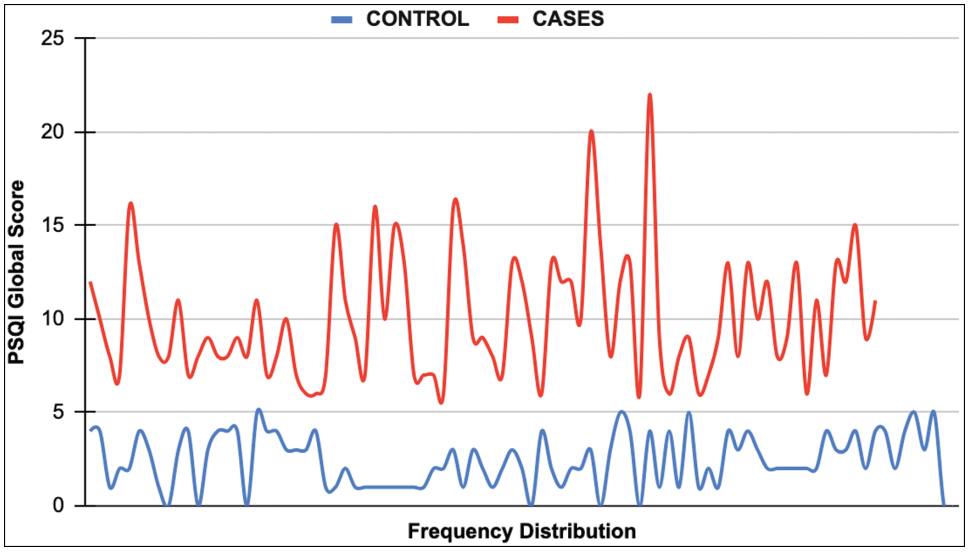


Figure 3: Frequency distribution of PSQI global scores among cases and controls

Table 3: The mean and SD of screen time and PSQI global score profile among cases and controls

Mean and SD	Screen time	PSQI global score
Cases (*n* = 89)	31.44 ± 13.06	8.64 ± 4.42
Controls (*n* = 78)	7.86 ± 3.63	3.2 ± 2.46

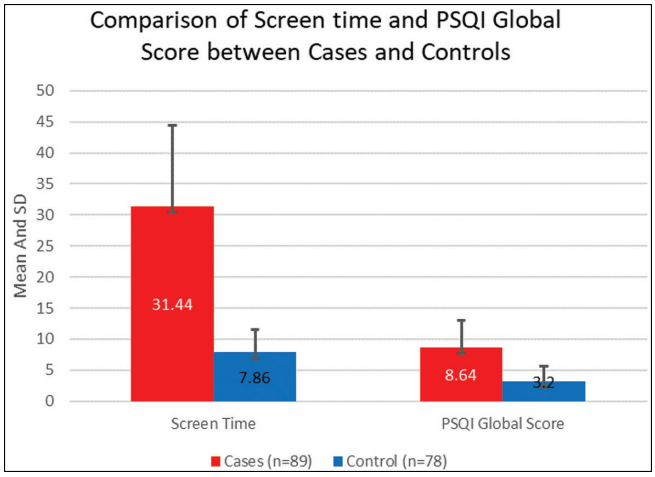


Figure 4: Comparison of screen time and the PSQI global score among cases and controls

As shown in Table 4, considering the PSQI global score, the mean score in cases is 8.64, while in controls it is 3.2. Subsequently, the mean difference in screen time is 5.44, and this is statistically significant. This was confirmed using an independent *t* test with the value of $t = 9.63$ at P value < 0.0001, indicating a highly statistically significant difference [Table 4].

The Spearman's correlation test was applied between the screen time and the PSQI global score. The resulting Spearman's rho value was 0.623, with a P value of <0.001 at 165 degrees of freedom and a 95% confidence interval. These results indicated a significant positive correlation between excessive screen time and abnormal PSQI scores in adolescents.

The chi-square test was calculated, resulting in a χ^2 value of 53.4, with a P value of <0.001 at a 95% confidence interval with 2 degrees of freedom. Hence, the adolescents who reported excessive screen time were more likely to have abnormal PSQI scores compared to those with lower screen time.

Table 4: Comparison of the PSQI global score between cases and controls

Sleep quality scale	Cases (n = 89)	Control (n = 78)	Mean difference	Unpaired t test
	Mean ± SD	Mean ± SD		
PSQI Global score	8.64±4.42	3.2±2.46	5.44	P< 0.0001***

***statistically highly significant

The relevance of these results lies in providing normative data for nerve conduction parameters in healthy individuals, particularly focusing on the upper limb and the median nerves. The studies show that arm, forearm length, and wrist circumference can affect sensory nerve conduction parameters, such as amplitude, latency, and velocity, with variations observed between males and females. The data serves as a reference for neurophysiological laboratories in assessing nerve abnormalities and diagnosing peripheral nerve diseases. The results highlight the importance of considering gender and age stratification when interpreting nerve conduction study results, as these parameters can influence normative values. The studies contribute to the existing literature on nerve conduction studies and provide valuable information for accurate diagnosis and assessment of nerve function in specific populations, such as the Nadia region of West Bengal, India, and Indian subjects, in general.

DISCUSSION

Excessive screen time has been consistently linked with poor sleep quality and an increased risk of sleep disorders. Research indicates that individuals who spend more than 6 h per day on screens are at a higher risk of experiencing sleep disturbances compared to those with screen time of 2–6 h per day. Farhana *et al.*[17] investigated the relationship between smartphone screen time and the PSQI among preclinical medical students and found that there are positive correlations between smartphone addiction tendencies, low sleep quality, academic procrastination, and academic burnout. This study identified that students with a screen time of more than 6 h per day have a 2.44 times greater risk of sleep disorders compared to those with a screen time of 2–6 h per day. In our study, the screen time of 2 h per day shows a potentially adverse effect on the quality of sleep as well as a positive correlation with PSQI global scores.

Krystel *et al.*[18] found that spending more than 4 h daily in front of screens decreased sleep duration and quality, particularly on weekdays. Downing *et al.*[19] discussed the concurrent trajectories of outdoor time, screen time, and sleep during early childhood, identifying four trajectories, including one with high screen time and high sleep. Maternal factors were found to be associated with group membership.

Santiago *et al.*[4] investigated that excessive screen time exposure is significantly associated with poor sleep quality. They also identified the association between sedentary screen time and sleep quality in adolescents, particularly noting that increased interaction with screens, such as video games and computers, could negatively impact sleep quality, particularly in adolescents with a higher risk of anxiety. Thus, sleep quality partially mediates the association between screen time and negative emotions, such as depression, anxiety, and stress. Therefore, excessive screen time users are more likely to experience poor sleep quality and an increased risk of sleep disorders. Screen time being a modifiable risk factor for poor quality sleep patterns, it should be prioritized as part of lifestyle modification.

This study analyzed data from 38 countries and revealed that higher levels of recreational screen use, both active and passive, were associated with sleep-onset difficulties among adolescents. Sleep is associated with difficulty in waking, affecting the quality of the sleep.[20] Similarly, in our study, the component of the PSQI indicated difficulties in waking up (sleep latency) among excessive screen time users.

Zhu *et al.*[21] found a J-shaped association between television viewing time and sleep disorder. The risk of sleep disorder increased by 12.35% for each 1 h per day increment in TV viewing time beyond the threshold of 1 h per day. Our study found that 2 h per day is affecting sleep quality, which investigates the impact of screen time on sleep disorders in preschool children.

Muhammad *et al.*[22] reported a mean total sleep duration of 6.7 ± 1.5, with 71% of students experiencing poor sleep quality. They found a relationship between screen time and sleep quality among college and university students in Karachi. They found that students who had more than 2 h of screen time on weekdays and weekends had a higher likelihood of poor sleep quality. These results support the outcome of the present study.

Dipika *et al.*[23,24] studied the correlation between screen time and sleep quality using the PSQI questionnaire and found a prevalence of 79% of increased screen time with PSQI scores of more than 5. They also observed the association between increased screen time and high PSQI scores as observed in the present study. Tezol *et al.*[25,26] reported excessive screen time and lower psychosocial well-being among preschool children. Freedman and Burke [26] and

García-Hermoso *et al.*[27] reported developmental hindering due to excessive screen time.

CONCLUSION

Collectively, these results provide comprehensive insight into the crossmodal effects on the quality of sleep, demonstrating that excessive screen time significantly impacts sleep quality, which can be assessed through simple questionnaire-based self-assessments. In conclusion, the findings of this study highlight the hazards of screen exposure on the quality of sleep in adolescents. This study suggests that adolescents with excessive screen time may exhibit differences in the development of sleep-related disorders compared to those with less screen time.

LIMITATIONS

This study has limitations regarding the population under study, as only those visiting the centers were included. This limitation hindered us from the calculation of the prevalence of excessive screen time and high PSQI global scores. This study did not take into account the time of exposure to screen time, as there were wide variations in time consistency for the usage of gadgets.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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Original Article

Six-Minute Walk Test among obese and nonobese subjects: A comparative analysis among apparently healthy volunteers

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Abstract

Context: The Six-Minute Walk Test (6MWT) is a simple measure for objective assessment of physical fitness and exercise tolerance. It has also been standardized to follow up on the prognosis and progression of chronic cardiovascular and respiratory diseases. Though there are standardized formulas for analyzing the 6MWT results concerning age, height, weight, regional, and ethnic population these should be revisited considering the wider variations of subjects in the reference studies.

Aim: This article aims to compare the 6MWT performance among obese and nonobese, apparently healthy volunteers.

Settings and Design: A cross-sectional study was conducted in the Physiology Department, AIIMS Kalyani, West Bengal, India.

Materials and Methods: Age and sex-matched apparently healthy volunteers were included in the study after their consent. After collection of anthropometric data, they were divided into two groups; group A with body mass index (BMI) $<30\,kg/m^2$ and group B with BMI $>30\,kg/m^2$. The 6MWT was implemented according to standard guidelines; the Six-Minute Walk Distance (6MWD) and other parameters were noted. Statistical analysis was performed by Statistical Package for the Social Sciences software version 17 (IBM Corp., Chicago, IL, USA).

Results: The results revealed that a comparison was done between actual values and predicted values of 6MWD. Among obese groups, the actual 6MWD covered was significantly lesser than the predicted values. Significant differences were also found between the two groups concerning Borg score, Calculated volume of oxygen max, systolic and diastolic blood pressures, respiratory rate, heart rate, and Peripheral capillary oxygen saturation.

Conclusions: The results revealed that our result shows that the weight-based reference equation for interpretation of 6MWT may not be sufficient for obese subjects.

Keywords: Exercise capacity, functional capacity, obesity, Six-Minute Walk Test

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INTRODUCTION

The Six-Minute Walk Test (6MWT) is a widely used clinical assessment tool that provides valuable insights into an individual's functional capacity and overall physical performance. Due to its simplicity, safety, and cost-effectiveness, the 6MWT has become an essential measure in various medical settings, including cardiology, pulmonology, and rehabilitation. It is the only test, in which functional capacity has been used as a factor for clinical assessment.[1] Six-Minute Walk Distance (6MWD) is the primary outcome of the test. Studies have shown that the 6MWD is very effective in predicting survival, mortality, and morbidity in patients with chronic respiratory diseases. A 6MWD of <350 m indicates an increased risk for hospitalization in chronic respiratory disease.[2] Research studies have established standard reference equations for the prediction of 6MWD based on age, height, weight, ethnicity, and gender. In India, Palaniappan and Chandrashekaran[3] have proposed a standard reference equation to calculate the ideal 6MWD. However, the mean body mass index (BMI) of the subjects included in this study was 20–29 kg/m^2. Therefore, the effect of BMI >30 kg/m^2 may not be optimally represented in this study.

In recent years, it has been reported that obesity has a significant impact on physical functioning and exercise capacity. Obesity has become a global health concern, and its prevalence has risen dramatically in both developed and developing countries.[4,5] It is established that obesity can independently decrease exercise tolerance, so investigating the differences in 6MWT outcomes between obese and nonobese individuals should be considered while interpretation. We have used the standard criteria of BMI to define obesity. According to the World Health Organization, we have considered subjects with a BMI of 25.00–29.99 kg/m^2 as preobese and a BMI of 30.0–34.99 kg/m^2 as class I obese.[6]

In this study, we wanted to analyze the 6MWD, heart rate response, blood pressure changes, Peripheral capillary oxygen saturation (SpO_2), respiratory rate, volume of oxygen (VO_2) max, and Borg score among obese and nonobese apparently healthy volunteers, in response to 6MWT. We intend to shed light on the potential impact of obesity on functional capacity and identify any differences in their performances. The significance of this study lies in its potential to quantify the understanding of obesity-related effects on 6MWT and its further clinical interpretation.

SUBJECTS AND METHODS

Study design and participants

An observational, cross-sectional study was conducted in the Department of Physiology at All India Institute of Medical Sciences, Kalyani, West Bengal, India, between December 2022 and July 2023. In this study, we recruited two groups of volunteers; group A with participants with a BMI of <30 kg/m² and the other group B with obesity BMI ≥30 kg/m². Participants were selected based on specific inclusion criteria, such as age 18–50 years and absence of any significant cardiovascular, respiratory, or musculoskeletal conditions that could affect their ability to perform the test. Informed consent was obtained from all participants before their inclusion in the study. The study was carried out adhering to all the ethical guidelines according to the Declaration of Helsinki.

6MWT protocol

Pretest preparation

Before the test day, participants were provided with a detailed explanation of the 6MWT procedure. The subjects were asked to refrain from vigorous physical activity on the day of the test and to avoid caffeine and smoking for at least 2 h before the test. They were asked to wear comfortable dresses and properly fitted walking shoes.

Equipment

A flat smooth, straight, and obstacle-free walking course of 30 m was marked. A stopwatch or timer was used to measure the 6-min duration accurately. Digital blood pressure measuring apparatus to record blood pressure readings. A pulse oximeter was used to calculate SpO_2 and heart rate. The respiratory rate was also calculated before starting the test. The lap was counted in the worksheet. Other precautionary measures, such as chairs, oxygen cylinders, and automatic defibrillators, were kept ready as per standard guidelines.

Data collection

Anthropometric data (e.g., height and weight) of participants was measured before the test to calculate BMI. Vital signs (heart rate, blood pressure, and respiratory rate) were recorded at baseline, immediately after the test, and during the recovery period. 6MWD were documented. The Borg Scale was used to document any breathlessness.[7,8]

Procedure

Participants were instructed to rest for about 10 min on a chair near the starting point of the walking course. Baseline measurements of resting heart rate, blood

pressure, and respiratory rate were recorded. Participants were asked to start walking at a comfortable pace as soon as the test began. The timer was set at the start of the walk, and subjects were asked to walk as far down the length of the corridor as they could at their own pace for 6 min. Standardized encouragement was provided every 60 s during the test, with the following phrases: "You're doing well" and "Keep up the good work." All subjects performed the 6MWT for the first time with no warm-up period during the test; the number of laps completed by participants was counted each time they returned to the starting point. Blood pressure, heart rate, and respiratory rate were monitored immediately after the test was completed. The total distance covered by each participant during the test was measured.

Data were collected by single-trained researchers to ensure accuracy and consistency.

Study equations

The predictive 6MWD equations were as follows:[9]

Indian males: 561.022 − (2.507×age [years]) + (1.505 × weight [kg]) − (0.055 × height [cm])

Indian females: −30.425 − (0.809 × age [years]) − (2.074 × weight [kg]) + (4.235 × height [cm]

VO_2 max calculation: VO_2max prediction equation was as follows:[10]

VO_2 max (mL/kg/min) = 12.701 + (0.06 × 6MWD m) – (0.732 × BMI kg/m^2)

Data analysis

Descriptive statistics was used for analyzing participants' baseline data. The 6MWDs were analyzed and compared between the obese and nonobese groups with predicted distances. Vital signs (heart rate, blood pressure, and respiratory rate) were compared before and after the test between the groups. Statistical tests were applied to determine significant differences between obese and nonobese groups. $P < 0.05$ was taken as statistical significance.

RESULTS

There is no statistically significant difference in the demographic variables, such as age and height, with a P value of >0.05. There was a highly statistically significant difference in the demographic variables, such as weight and BMI, with a P value of <0.0001 [Figures 1–7].

In this present study, Table 1 depicts the comparison of two groups according to demographic variables. It was found that all the parameters had their mean differences. An unpaired t test was applied. The age and height were statistically nonsignificant but the weight and BMI results were significant at 0.05 level of significance.

Table 2 shows the comparison of two groups according to clinical variables before and after 6MWT. During the pretest, there was a significant difference between diastolic blood pressure (DBP), respiratory rate, and heart rate between the groups. Posttest, systolic blood pressure (SBP), DBP, respiratory rate, and SpO_2 become significant. Unpaired t test was applied at a $P < 0.05$ level of significance.

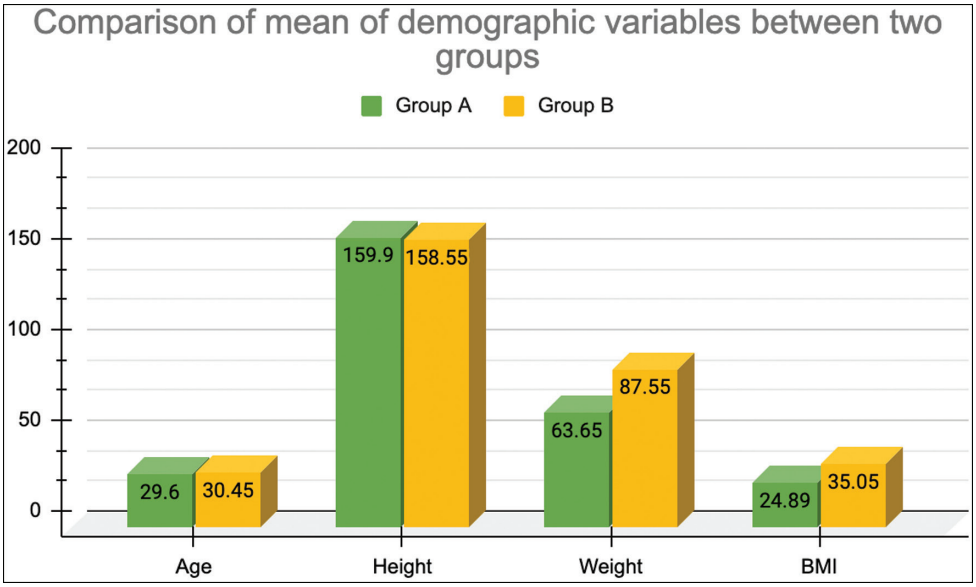

Figure 1: Bar diagram showing a comparison of demographic variables between the groups

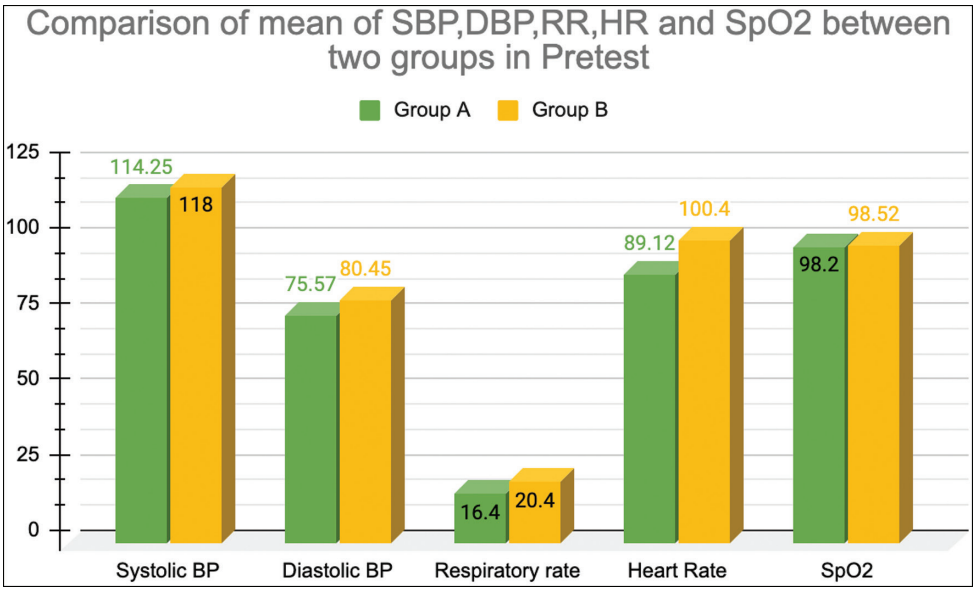

Figure 2: Bar diagram showing comparison of clinical variables between the groups before 6MWT

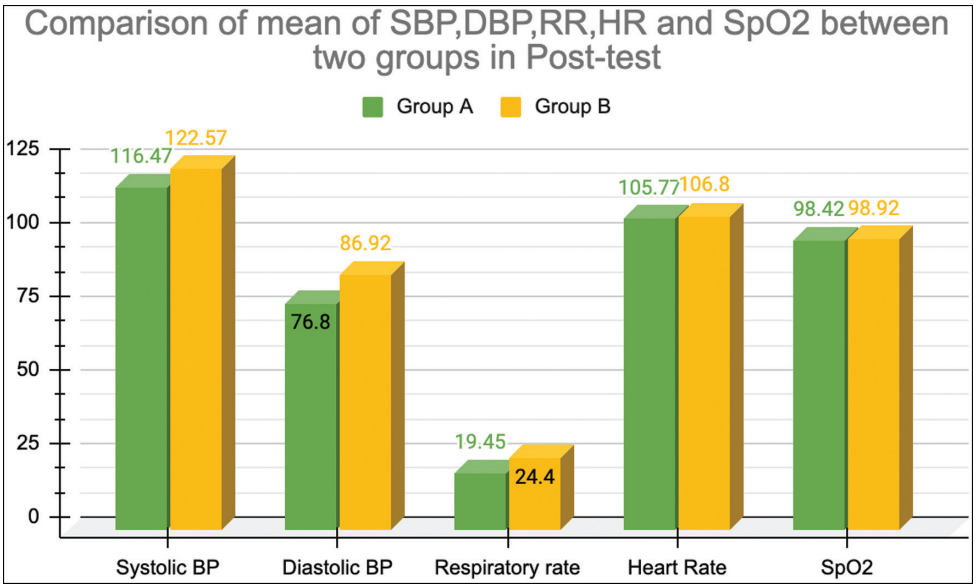

Figure 3: Bar diagram showing comparison of clinical variables between the groups after 6MWT

Table 3 depicts the comparison of two groups according to the BORG scale and calculated VO_2 max. It was found that all the parameters had their mean differences. Unpaired *t* test was applied at a $P < 0.05$ level of significance.

Table 4 depicts the comparison of actual and predictable 6MWD in the female and male population in each group. It was found that there is an extremely significant statistical difference in actual and predictable distances in group B for both female and male subjects. There were no statistically significant differences in actual and predictable distance in group A. One sample *t* test was applied at a $P < 0.05$ level of significance.

Table 5 depicts the comparison of Actual 6MWD in female and male populations in each group. It was found that there was an extremely significant statistical difference in distances in each group. Unpaired *t* test was applied at a $P < 0.05$ level of significance.

DISCUSSION

In this study, we found that significant variations exist in the 6MWT outcomes between obese and nonobese participants. First, the 6MWD was significantly lower in the obese group compared with the nonobese group. The reduction in 6MWT performance in obese subjects could

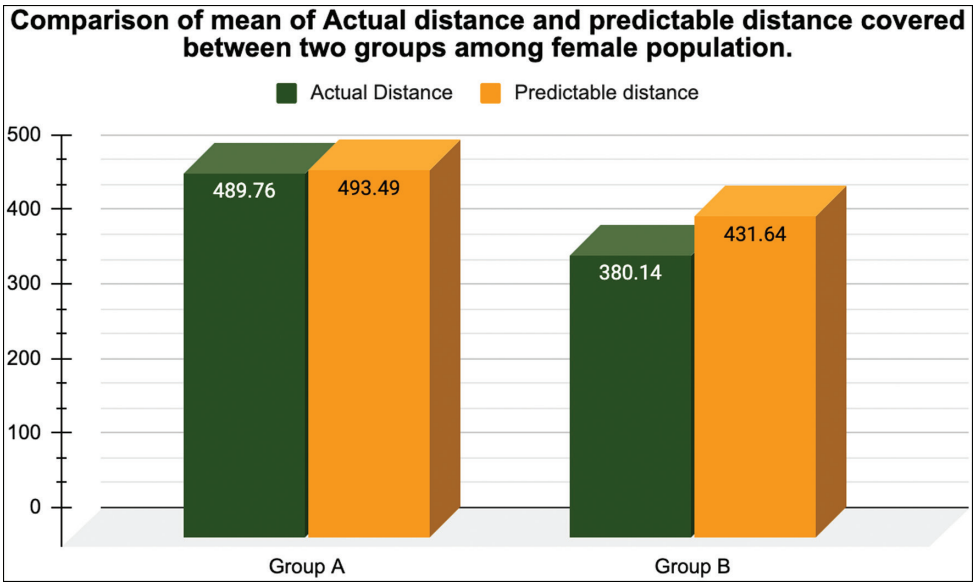

Figure 4: Bar diagram showing a female gender-wise comparison of actual and predictable 6MWD between the groups

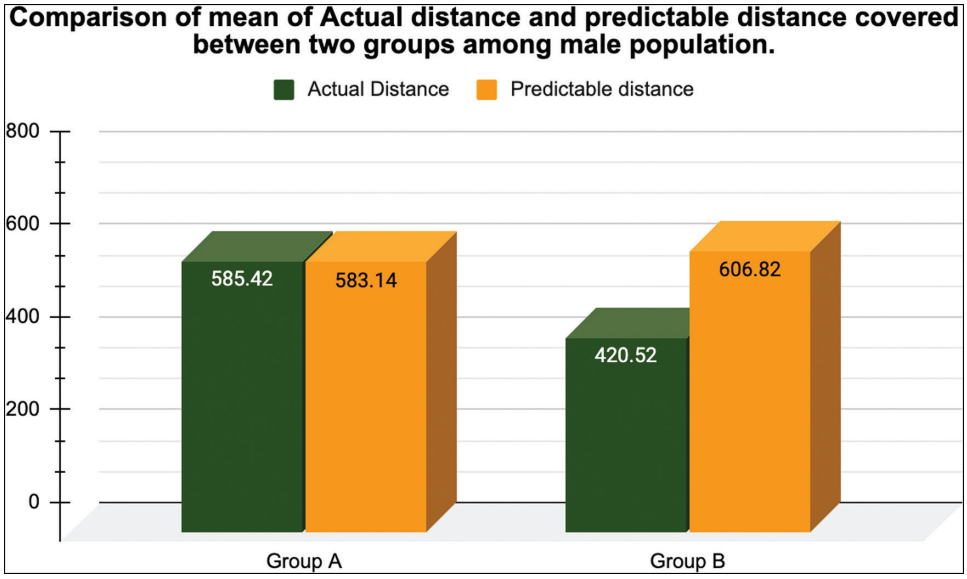

Figure 5: Bar diagram showing a male gender-wise comparison of actual and predictable 6MWD between the groups

be attributed to several physiological factors. Second, excess adiposity places additional strain on the cardiovascular system, leading to decreased cardiac output and impaired oxygen delivery to tissues during exercise. Third, the increased weight and mechanical load on the lower limbs can result in muscle fatigue and reduced efficiency of movement during the test. Finally, obese individuals often experience reduced pulmonary function, which limits their ability to exchange oxygen and carbon dioxide effectively during physical activity.

We also observed significant differences in the heart rate, blood pressure, and respiratory rates following 6MWT between the two groups. Obese individuals exhibited higher resting heart rates and higher resting diastolic blood pressure. Following the test, the increment of heart rate and Blood pressure was higher in obese subjects compared with nonobese subjects. Obese individuals tended to have a higher respiratory rate both at resting and after the test, indicating potential difficulties in respiratory function and breathing efficiency. Decreased cardiorespiratory fitness of the obese group may have contributed to reduced exercise capacity. Increased cardiovascular and respiratory difficulties were also reflected by the significant Borg score and calculated $VO_{2\,max}$ among the obese group compared with the nonobese group. Shanmugasundaram *et al.*[11] has shown obesity/overweight causes significant changes in lung volumes, capacity, and airway mechanics, and the

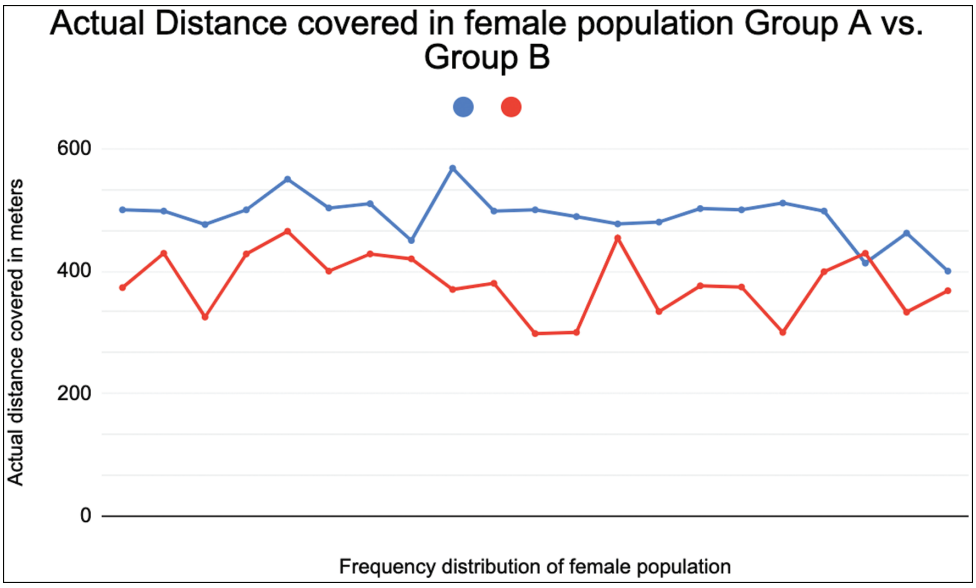

Figure 6: Frequency distribution showing actual distance of 6MWT among the female population

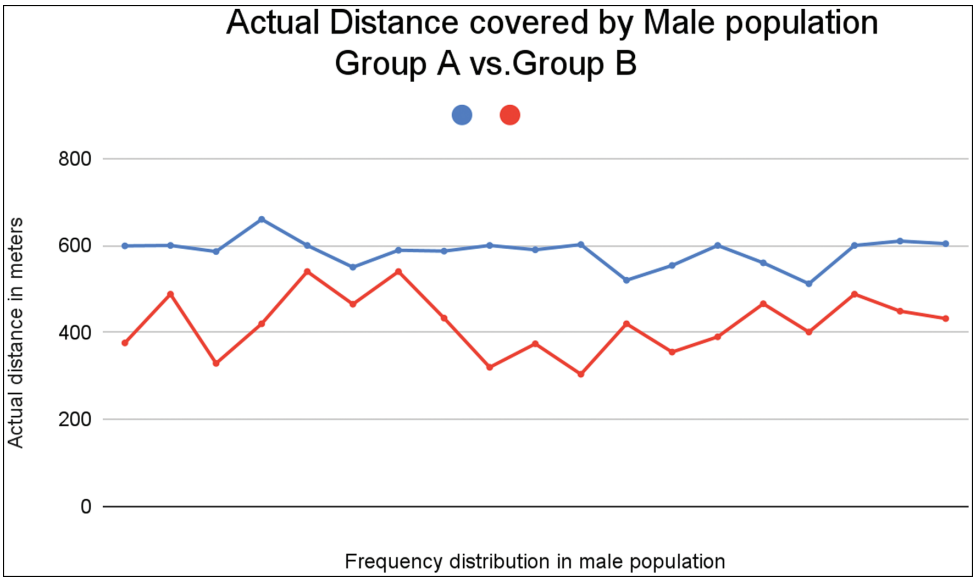

Figure 7: Frequency distribution showing actual distance of 6MWT among the male population

effect is more pronounced in females compared with males. Previous studies by Carli *et al.*,[12] Dixon *et al*,[13] and Shete *et al.*[14] have shown the effect of obesity was based on heart rate, VO_2 max, and cardiovascular fitness. 6MWT, which is considered to be a submaximal physical function test for nonobese subjects, may be maximal for obese subjects.

We also found that there is a significant reduction in actual 6MWD in the obese group, both in females and males, compared with predicted 6MWD. We used the reference equation proposed by Palaniappan and Chandrashekaran[3] for the calculation of 6MWD. This is the only reference equation for Indian subjects, in which weight is an independent factor for the calculation of 6MWD. There are two other reference equations by Vaish *et al.*[15] and Agarwal *et al.*,[16] for calculation of 6MWD for Indian subjects. However, in all of these studies the average BMI was below 30 kg/m^2, so none of these studies has the result of the effect of obesity on 6MWT. Therefore, these reference equations may not be sufficient to reflect the effect of 6MWT in obese subjects.

The word "apparently" (Collins Dictionary) indicates that the information given is something that is, heard, but not certain it is true. The obese population, in our study, did not have any diagnosed major illnesses, such as diabetes, hypertension, metabolic syndrome, or on any medications. Although obesity itself is a condition affecting the normal physiology.[17]

Table 1 : Comparison of demographic variables between the groups

Variables	Group A (n = 40) Mean ± SD	Group B (n = 40) Mean ± SD	Unpaired t test (DF = 78)
Age	29.6 ± 5.38	30.45 ± 7.95	t = 0.56, P = 0.57 (NS)
Height	159.9 ± 4.52	158.55 ± 7.24	t = 1, P = 0.32 (NS)
Weight	63.65 ± 6.20	87.55 ± 10.84	t = 12.1, P < 0.0001***
BMI (kg/m^2)	24.89 ± 2.20	35.05 ± 3.08	t = 16.97, P < 0.0001***

DF: degree of freedom, NS: not significant (P > 0.05).
***Extremely significant = $P \leq 0.0001$

Table 2: Comparison of SBP, DBP, HR, respiratory rate, and SpO2 between the groups in pretest and posttest

Assessments		Group A (n = 40) Mean ± SD	Group B (n = 40) Mean ± SD	Unpaired t test DF = 78
Pretest	SBP	114.25 ± 7.91	118 ± 8.98	t = 1.98, P = 0.51 (NS)
	DBP	75.57 ± 9.17	80.45 ± 8.14	t = 2.51, P = 0.013*
	Respiratory rate	16.4 ± 1.80	20.4 ± 2.57	t = 8.21, P < 0.0001***
	HR	89.12 ± 15.42	100.4 ± 15.76	t = 0.3.23, P = 0.0018*
	SpO_2	98.2 ± 1.09	98.52 ± 0.55	t = 1.65, P = 1.101 (NS)
Posttest	SBP	116.47 ± 9.48	122.57 ± 11.71	t = 2.56, P = 0.012*
	DBP	76.8 ± 7.89	86.92 ± 6.75	t = 6.16, P < 0.0001**
	Respiratory rate	19.45 ± 2.79	24.4 ± 3.09	t = 7.51, P < 0.0001***
	HR	105.77 ± 20.40	106.8 ± 18.05	t = 0.23, P = 0.81 (NS)
	SpO_2	98.42 ± 1.00	98.92 ± 0.26	t = 3.06, P = 0.003*

SBP: systolic blood pressure, DBP: diastolic blood pressure, HR: heart rate, SpO_2: oxygen saturation (on room air), NS: not significant (P > 0.05), DF: degree of freedom.
*Significant = P < 0.05.
**Very high significant = $P \leq 0.001$.
***Extremely significant = $P \leq 0.0001$

Table 3: Comparison Borg score and calculated VO_2 max between the groups

	Group A (n = 40) Mean ± SD	Group B (n = 40) Mean ± SD	Unpaired t test
BORG score	0.67 ± 0.93	2.13 ± 1.10	t = 6.38, P < 0.0001***
Calculated VO_2 max	25.47 ± 5.81	11.00 ± 4.56	t = 12.39, P < 0.0001***

NS: not significant (P > 0.05).
***Extremely significant = $P \leq 0.0001$

Table 4: Gender wise comparison of actual and predictable 6MWD between the groups

Groups		Actual 6MWD Mean ± SD	Predicted 6MWD Mean ± SD	One sample t test
Group A	Female (n = 21)	489.76 ± 37.62	493.49 ± 18.98	t = 0.4, P = 0.65, DF = 20 (NS)
	Male (n = 19)	585.42 ± 33.85	583.14 ± 16.69	t = 0.32, P = 0.75, DF = 18 (NS)
Group B	Female (n = 21)	380.14 ± 50.83	431.64 ± 21.45	t = 4.64, P = 0.0002**, DF = 20
	Male (n = 19)	420.52 ± 68.56	606.82 ± 26.67	t = 11.84, P = 0.0001***, DF = 18

DF: degree of freedom, NS: not significant (P > 0.05).
**Very high significant = $P \leq 0.001$.
***Extremely significant = $P \leq 0.0001$

Obesity has been shown to have a significant impact on pulmonary function. The effects of obesity on lung function are attributed to both mechanical factors and complex metabolic effects that contribute to a pro-inflammatory state.[18] Studies have demonstrated that an increased BMI is associated with a decrease in forced expiratory volume in 1 s, indicating impaired pulmonary function.[19] Obese individuals often experience marked decreases in expiratory reserve volume and functional residual capacity, whereas total lung capacity, residual volume, and spirometry are generally within the normal range.[20] Additionally, obesity is associated with impaired gas transfer, with decreases in oxygenation and varied effects on diffusing capacity for carbon monoxide.[13] These findings suggest that obesity can limit the ability of individuals to effectively exchange oxygen and carbon dioxide during physical activity.[21]

The physiological differences between obese and normal-weight individuals during the 6MWT can indeed be a crucial aspect to consider in research and clinical settings. The 6MWT is a commonly used measure of

Table 5 : Gender wise comparison of actual 6MWD between two groups

Actual distance	Group A		Group B		Unpaired *t* test
	Mean	SD	Mean	SD	
Female	489.76	37.62	380.14	50.83	$t = 7.94$, $P < 0.0001^{***}$, DF = 40
Male	585.42	33.85	420.52	68.56	$t = 9.4$, $P < 0.0001^{***}$, DF = 36

DF = degree of freedom, NS: not significant ($P > 0.05$).
***Extremely significant = $P \leq 0.0001$

functional exercise capacity and cardiovascular fitness. Here are some potential physiological differences that might need to be considered when comparing obese and normal-weight groups in the context of the 6MWT. In the cardiovascular system, the cardiac output in obese individuals may have a higher resting condition due to increased blood volume and higher metabolic demands associated with excess body mass. The heart rate response to exercise may differ, with obese individuals potentially exhibiting a different heart rate pattern during and after the 6MWT. In respiratory function, ventilation in obese individuals often experiences altered lung mechanics and reduced lung compliance, which can affect ventilation and respiratory efficiency during exercise. The oxygen consumption in resting and exercise situations may be higher in obese individuals due to increased metabolic demands associated with supporting a larger body mass. In the musculoskeletal system, obesity can be associated with decreased muscle strength and endurance, potentially influencing performance during the 6MWT. Obese individuals may experience increased stress on weight-bearing joints, affecting mobility and exercise performance. Obese individuals may have higher energy expenditure at rest and during physical activity, influencing their ability to sustain exercise intensity during the 6MWT. Differences in basal metabolic rate and substrate utilization may affect energy metabolism during the test. In the psychosocial factors, obese individuals may perceive exercise differently, and their perceived exertion during the 6MWT could be influenced by factors, such as body image, self-esteem, or psychological well-being. Obesity can impact thermoregulation, potentially affecting exercise performance, especially in environments with varying temperatures.

Thus, moderate-to-vigorous 6MWT may help determine an individual's level of aerobic fitness, which is linked to various health confounding variable consequences. The predictive value of the 6MWT for calculating VO_2 max is significantly increased when additional patient variables are included. This has significant implications for people looking for a straightforward and noninvasive method of determining maximal aerobic power.[22,23] Considering these factors is crucial when interpreting and comparing 6MWT results between obese and normal-weight groups. We should account for these potential confounding variables and may need to adjust their analyses or control for relevant physiological differences to draw meaningful conclusions in future studies.

Novelty

This research gives a simple cost-effective approach to assess the calculated VO_2 max and Borg scale for breathlessness in obese populations. This can help the obese population understand the need for preventive measures to be taken even if they have no symptoms of any cardiopulmonary insufficiency. These data are indicative of the comparative difference in their cardiopulmonary insufficiency in these two groups and hence worth predicting the chances of lifestyle-related disorders in the obese population.

Limitations

Limitations of our study include a relatively small sample size and potential confounding factors that were not fully controlled. Future studies with larger and more diverse populations are needed to validate our findings further. Additionally, longitudinal studies could help establish causality and investigate the effects of weight loss interventions on the 6MWT outcomes in obese individuals.

CONCLUSION

In conclusion, this study highlights the significant impact of obesity on exercise capacity and physical functioning as assessed by the 6MWT. Obese subjects demonstrated reduced distance covered during the test, altered heart rate responses, and changes in respiratory rate, indicating potential impairments in cardiopulmonary and musculoskeletal function. These findings emphasize the importance of addressing obesity-related limitations in exercise capacity through personalized interventions to enhance overall health and quality of life. 6MWT is a valuable and accessible tool to assess exercise tolerance and follow-up cardiovascular fitness among chronic respiratory disease patients. However, this study suggests that obesity is associated with reduced 6MWT performance among healthy subjects, and present reference equations, used for interpretation of 6MWT, may not be sufficient

to interpret cardiovascular fitness among obese patients. Further research is needed to standardize the base reference equation of 6MWT for the obese Indian population, which may be applied to the interpretation of 6MWT in clinical and experimental situations.

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Conflicts of interest

There are no conflicts of interest.

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Original Article

Cognitive impairment is associated with female sex, low level of education, lack of spousal relationship, and serum testosterone in type 2 diabetes

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Abstract

Background: Relationship between cognitive impairment, serum testosterone, and body mass index in type 2 diabetes (T2D) is not fully understood.

Objectives: To compare cognition between T2D patients and healthy controls. To determine relationship of mild cognitive impairment (MCI) with serum total testosterone and sociodemographic factors.

Materials and Methods: The study was a cross-sectional case-control study. About 17 male and female T2D patients and healthy controls were randomly selected. Montreal cognitive assessment-basic (MoCA-B) was used to assess cognition; anthropometric indices were measured using standard protocols, while total testosterone was assayed from serum using competitive ELISA kits.

Results: The mean age of the T2D patients and healthy controls was 51.62 and 66.76 years, respectively. About 82.35% of the T2D patients had MCI compared to 58.82% of the healthy controls. MCI was associated with female sex ($P = 0.033$), lack of spousal relationship ($P = 0.016$), low level of education ($P = 0.014$), and normal or high level of total testosterone ($P = 0.010$).

Conclusion: Proportion of MCI in T2D patients is high and is associated with female sex, lack of spousal relationship, low level of education, and normal or high testosterone level.

Keywords: Mild cognitive impairment, obesity, sub-Saharan Africa, testosterone, type 2 diabetes

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INTRODUCTION

Global prevalence of T2D has more than tripled in the last three decades, and by 2030 and 2045, about 11% and 12% of world population will be living with diabetes, respectively.[1] In sub-Saharan Africa (SSA), about 24 million persons were said to have diabetes in 2021, and the figure has been projected to rise by over 120% by the year 2045, the largest increase in any region of the world.[1]

Similarly, efforts at combating the scourge of infectious diseases and improvement in science and technology have led to increase in life expectancy across all regions of the world, especially low- and middle-income countries.[2] Thus, SSA will in the near future be faced with problems of rising prevalence of T2D and age-associated health issues. Both aging and T2D have been linked with mild cognitive impairment (MCI), a decline in cognition

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between the normal aging process and dementia.[3–5] This gradual decline in cognitive function has been identified as a risk factor for dementia.[6] Incidentally, T2D and MCI have separately been linked to low levels of testosterone and other sociodemographic factors.[7–9] Low level of testosterone is believed to increase insulin resistance and hence T2D.[10] Similarly, testosterone receptors have been demonstrated in areas of the brain involved in cognitive function, suggesting that testosterone could improve cognition; however, testosterone supplementation trials have produced mixed results.[11,12] Additionally, relationship between body mass index (BMI), an index of obesity, and MCI is inconsistent and classified into no relationship,[13] positive relationship,[14,15] negative relationship,[16,17] a reverse J-shaped relationship,[18] and a U-shaped relationship.[19]

AIMS AND OBJECTIVES

To compare cognition between T2D patients and healthy controls. To determine the relationship of MCI with serum total testosterone and other sociodemographic factors.

MATERIAL AND METHODS

The participants

The study was a cross-sectional case-control study. The participants were T2D patients attending the Diabetic Clinic of Murtala Muhammad Specialist Hospital (City Hospital), Kano, Nigeria, while the controls were community-dwelling healthy individuals. Both the diabetics and the controls came from the same community and are a reflection of a typical northern Nigerian community. A systematic random sampling was used to recruit the participants. Each participant was initially medically examined, those with a history of hypertension, other endocrine disorders, depression, sexual dysfunction, and visual or hearing impairment were not included in the study. Each participant gave written informed consent.

Ethical approval

Ethical approval was obtained from Kano State Ministry of Health through the Health Research Ethics Committee (SHREC/2022/3740, dated 24 Jan 2023).

Sample size determination

G*Power computer software version 3.1.9.7 was used to determine sample size.[20] Mean (*SD*) of serum testosterone among T2D patients (16.8 ± 7.07) and healthy controls (13.4 ± 7.70) from a previous study,[21] α level of significance of 0.05, an effect size of 0.46, and a statistical power of 0.84 were used, which gave 40.

Assessment of cognition

Montreal cognitive assessment-basic was used to assess cognitive function. The tool was developed for assessment of MCI in different settings, especially among participants with low level of education.[22,23] The tool has been widely used to assess cognitive function with good validity. A number of previous studies have used this tool to assess cognitive function among Nigerian participants.[5,24,25] A MoCA-B score of less than 26 was used a as cutoff score for MCI.

Measurement of some anthropometric indices

Weight and height were measured according to standard protocols using a digital weighing scale (Omron HN286, Kyoto, Japan) and a stadiometer, to the nearest 100 g, with the participants wearing light clothing, barefooted, without caps, and standing in anatomical position.[26] The weight and the height were then used to calculate BMI as weight (in kg) divided by height (in meters square).

Measurement of fasting blood glucose and blood pressure

Measurement of blood pressure was taken on left arms of the participants in sitting position, with a mercury sphygmomanometer (AccosonTM Ltd., Ayrshire, UK) and a Littmann stethoscope (3M Littmann®, Minnesota, USA). The first Korotkoff sound was used as systolic blood pressure, while its disappearance was taken as diastolic. An on-site Accu-Chek® (Roche Diabetes Care, Inc., Indianapolis, USA) glucometer was used to measure fasting blood glucose (FBG) after an overnight fast.

Measurement of serum total testosterone

About 5 mL of blood sample was withdrawn from each participant between 8 and 9 AM following an overnight fast. The sample was centrifuged at 1000 g for 10 min to extract the serum, which was stored at −20°C. The serum total testosterone was determined using competitive ELISA kits from CALBIOTECH (El Cajon, California, USA). The test is based on competitive binding of total testosterone in samples with their enzyme conjugates for a constant amount of specific monoclonal antibody epitopes (Biotin reagent). The total testosterone ELISA kit has a detection rate of 0.25–100 pg/mL, sensitivity of 1.16 pg/mL, and intra- and interassay coefficient of variation of 3.72% and 6.90%, respectively. A low serum total testosterone was defined according to a previous guideline.[27]

Statistical analysis

The data were analyzed using an SPSS version 23.0. The quantitative variables were presented as mean (*SD*), while categorical variables as frequencies (%). Independent

sample *t* test was used to determine a difference in quantitative variables between T2D patients and controls; a Chi-square test of association was used to assess association between categorical variables; a Pearson's correlation to assess linear relationship between quantitative variables, and a binary logistic regression to determine the predictors of MCI. *P* value is taken as ≤0.05.

RESULTS

Characteristics of the participants stratified by cognitive function and T2D statuses

An equal number[17] of male and female T2D patients and controls were recruited for this study. Their characteristics, stratified by cognitive function and T2D statuses, are presented in [Tables 1 and 2] and summarized here. The T2D patients were statistically and significantly younger (mean age = 51.62 ± 10.92 vs. 66.76 ± 7.37 years; $P \leq 0.001$), heavier (weight = 66.89 vs. 57.71 kg; $P = 0.003$), overweight (BMI = 26.77 vs. 22.39 kg/m^2; $P \leq 0.001$), and had poorer cognitive function score (MoCA-B score = 18.24 vs. 20.21; $P = 0.021$). Similarly, T2D was associated with higher level of formal education ($P = 0.004$), low annual income ($P = 0.029$), overweight and obesity ($P = 0.004$), and MCI ($P = 0.033$). Female T2D patients had statistically significant lower serum total testosterone compared to female controls (0.46 vs. 0.84 nmol/L; $P = 0.038$); however, there was no difference among male participants even though mean serum total testosterone in both groups was low. The levels of serum total testosterone were also not associated with T2D ($X^2 = 0.24$; $P = 0.625$).

The participants were categorized into cognitively normal versus MCI groups, based on MoCA score. When the participants were considered as a whole, the MCI

Table 1: Characteristics of the participants by T2D status

Variable	Controls (n = 34)		Type 2 diabetics (n = 34)			
	N/Mean	%/SD	N/Mean	%/SD	X²/t	P
Age (years)	66.76	7.37	51.62	10.95	6.69	<0.001
Marital status						
Married	23	(67.65)	24	(70.59)	0.07	0.793
Unmarried	11	(32.35)	10	(29.41)		
Level of education						
Formal	10	(29.41)	22	(64.71)	8.50	0.004
Informal	24	(70.59)	12	(35.29)		
Estimated annual income						
<$200	13	(38.24)	22	(64.71)	4.77	0.029
≥$200	21	(61.76)	12	(35.29)		
Blood pressure categories						
Normal	20	(58.82)	21	(61.76)	0.06	0.804
Elevated	14	(41.18)	13	(38.24)		
BMI categories						
Underweight	5	(14.71)	1	(2.94)	10.95	0.004
Normal	21	(61.76)	12	(35.29)		
Overweight/obesity	8	(23.53)	21	(61.76)		
MoCA-B						
Normal	14	(41.18)	6	(17.65)	4.53	0.033
MCI	20	(58.82)	28	(82.35)		
Testosterone categories						
Normal	16	(47.06)	14	(41.18)	0.24	0.625
Low	18	(52.94)	20	(58.82)		
Education (years)	2.88	5.01	5.32	5.48	−1.92	0.060
Systolic blood pressure (mm Hg)	127.94	26.72	130.29	18.83	−0.42	0.676
Diastolic blood pressure (mm Hg)	73.53	16.86	79.12	11.11	−1.61	0.111
Mean arterial pressure (mm Hg)	91.49	18.62	96.18	12.82	−1.21	0.231
Pulse pressure (mm Hg)	54.41	18.94	51.18	12.74	0.83	0.411
Fasting blood glucose (mmol/L)	5.56	0.78	8.79	3.57	−5.12	<0.001
Weight (kg)	57.71	13.28	66.89	11.33	−3.07	0.003
Height (m)	1.60	0.12	1.59	0.10	0.58	0.566
Body mass index (kg/m²)	22.39	3.90	26.77	4.82	−4.12	<0.001
MoCA-B score	20.21	3.57	18.24	3.32	2.36	0.021
Testosterone (nmol/L)*						
Males	7.38	3.85	8.29	4.20	0.65	0.524
Females	0.84	0.49	0.46	0.52	2.16	0.038

Categorical variables are presented as frequencies (*N*) and percentages (%) with associated Chi square values, while quantitative variables are presented as mean (*M*) and standard deviation (*SD*) with associated independent samples *t* test statistic.
MoCA-B: Montreal cognitive assessment-basic, T2D: type 2 diabetes, MCI: mild cognitive impairment.
*Because of sex-related differences in serum total testosterone, its mean value is presented separately for males and females

Table 2: Characteristics of the participants stratified by cognitive function

Variable	Normal (n = 20)		Mild cognitive impairment (n = 48)			
	N/Mean	%/SD	N/Mean	%/SD	X^2/t	P
Age (years)	58.70	8.22	59.40	13.34	−0.22	0.829
Sex						
Males	14	(70)	20	(41.67)	4.53	0.033
Females	6	(30)	28	(58.33)		
Marital status						
Married	18	(90)	29	(60.42)	5.79	0.016
Unmarried	2	(10)	19	39.58)		
Level of education						
Formal	14	(70)	18	(37.5)	5.99	0.014
Informal	6	(30)	30	(62.5)		
Estimated annual income						
<$200	5	(25)	30	(62.5)	7.95	0.005
≥$200	15	(75)	18	(37.5)		
Blood pressure categories						
Normal	13	(65)	28	(58.33)	0.262	0.609
Elevated	7	(35)	20	(41.67)		
BMI categories						
Underweight	3	(15)	3	(6.25)	1.63	0.443
Normal	10	(50)	23	(47.92)		
Overweight/obesity	7	(35)	22	(45.83)		
Testosterone categories						
Normal	4	(20)	26	(54.17)	6.69	0.010
Low	16	(80)	22	(45.83)		
Education (years)	7.10	5.83	2.85	4.66	3.17	0.002
Systolic blood pressure (mm Hg)	126.50	27.58	130.21	20.99	−0.60	0.548
Diastolic blood pressure (mm Hg)	72.50	18.32	77.92	12.37	−1.42	0.160
Mean arterial pressure (mm Hg)	90.37	20.49	95.27	13.78	−1.15	0.254
Pulse pressure (mm Hg)	54.00	16.03	52.29	16.27	0.40	0.693
Fasting blood glucose (mmol/L)	6.16	2.16	7.32	3.12	−1.45	0.151
Weight (kg)	62.26	11.02	62.31	13.98	−0.02	0.987
Height (m)	1.62	0.08	1.58	0.12	1.20	0.233
Body mass index (kg/m^2)	23.93	4.72	24.85	4.97	−0.70	0.483
Testosterone (nmol/L)*						
Males	7.55	4.16	8.05	3.97	−0.35	0.726
Females	0.31	0.23	0.73	0.55	−1.80	0.081

Categorical variables are presented as frequencies (*N*) and percentages (%) with associated Chi-square values, while quantitative variables are presented as mean (*M*) and standard deviation (*SD*) with associated independent samples *t* test statistic.
*Because of sex-related difference in serum total testosterone, its mean value is presented separately for males and females

group had lesser number of years of formal education ($P = 0.002$), were mostly females ($P = 0.033$), without spousal relationship ($P = 0.016$), had no formal education ($P = 0.014$), and had lower annual income ($P = 0.005$); other quantitative variables did not differ between the cognitively normal and MCI groups. Similarly, over 50% of those with MCI had normal or above normal serum total testosterone. Among the T2D patients, MCI was not associated with any characteristic of the T2D patients, neither did any quantitative variable differ between the cognitively normal and MCI groups.

Correlation between some parameters of the participants

We assessed the correlation of MoCA-B and serum total testosterone with other quantitative parameters of the participants and presented the results in [Table 3]. Among the whole participants, MoCA-B score was positively correlated with education ($P = 0.006$) and serum total testosterone ($P = 0.044$) but negatively correlated with FBG ($P = 0.017$); serum total testosterone was positively correlated with education ($P \leq 0.001$), height ($P = 0.009$), weight ($P \leq 0.001$), and BMI ($P = 0.019$) but negatively correlated with DBP ($P = 0.047$). Among T2D patients, MoCA-B did not correlate with any parameter; the serum testosterone was however positively correlated with education ($P = 0.001$), weight ($P = 0.018$), and BMI ($P = 0.047$) but negatively correlated with FBG ($P = 0.044$). Among the controls, MoCA-B was positively correlated with number of years of formal education ($P \leq 0.001$), weight ($P = 0.050$), and height ($P = 0.050$), and negatively correlated with age ($P \leq 0.001$), while serum total testosterone was positively correlated with the number of years of formal education ($P = 0.005$), height ($P = 0.001$), weight ($P = 0.001$), and MoCA-B score ($P = 0.041$) but negatively correlated with age ($P = 0.012$), DBP ($P = 0.014$), and MAP ($P = 0.035$).

Predictors of MCI among the participants

We used binary logistic regression to determine the possible predictors of MCI among the whole participants

and among the T2D patients. The results are presented in [Tables 4 and 5]. After controlling for possible confounders, a lack of spousal relationship (OR = 7.034 [1.847, 58.380]; $P = 0.041$), a lack of formal education (OR = 5.376 [1.150, 25.134]; $P = 0.033$), and a low total testosterone (OR = 0.164 [0.683, 0.013]; $P = 0.013$) were the statistically significant predictors of MCI among the whole group. Specifically, a lack of spousal relationship and formal education were associated with 7 and 5 times odds of having MCI, respectively; a low serum total testosterone is associated with 84% chance of having MCI. Among T2D patients, female sex ($P = 0.044$) and low number of years of formal education ($P = 0.035$) were the significant predictors of MCI.

DISCUSSION

This study assessed MCI in T2D and its possible association with serum total testosterone, BMI, and other sociodemographic factors. Despite being younger than the controls, the T2D patients had statistically significant higher proportion of those with MCI (82%) compared to the controls. Similarly, the T2D patients had statistically significant lower MoCA-B score compared to the controls. A number of studies have linked T2D with MCI. A cognitive impairment among T2D patients in this environment has been reported.[5,24] In a meta-analysis involving 34 neurocognitive and 60 neuroimaging studies, including complementary data from UK Biobank, Antal *et al.*[3] found T2D to be associated with marked cognitive deficits particularly in executive function and processing speed compared to sex, age, education, and hypertension-matched controls. They also reported structural changes in the brain such as gray matter atrophy affecting ventral striatum, cerebrum, and putamen. In another study involving 800 participants, a prevalence of MCI of 63.8% was reported against 10.8% among controls.[4] The finding of high proportion of MCI among T2D patients in this study calls for concern. Sub-Saharan Africa has been projected to have increasing number of people living with T2D in the near future; the life expectancy is also said to be on the increase in the continent and will continue to be so; the combined effects of rising prevalence of T2D and increasing number of elderly persons could potentially worsen the outlook of cognitive impairment, and indeed dementia, in the continent in the near future. Screening programs that can detect those with MCI and those at risk should therefore form a part of routine care of T2D patients in the continent. Areas of possible intervention from the findings of this study are economic empowerment especially for women, increasing access to formal education, and spousal relationship because the T2D patients with MCI had statistically significant higher

Table 3: Correlation of MoCA-B and serum total testosterone with some characteristics of the participants

Variable	Whole participants				Subgroup analysis							
					Controls				Type 2 diabetics			
	MoCA-B		T		MoCA-B		T		MoCA-B		T	
	r	P	r	P	r	P	r	P	r	P	r	P
Age	0.03	0.779	−0.03	0.839	−0.60	<0.001	−0.43	0.012	0.09	0.603	0.24	0.181
Education	0.33	0.006	0.49	<0.001	0.59	<0.001	0.47	0.005	0.26	0.142	0.53	0.001
SBP	−0.06	0.619	−0.08	0.497	−0.14	0.414	−0.23	0.189	0.10	0.590	0.09	0.622
DBP	−0.05	0.681	−0.24	0.047	−0.05	0.767	−0.42	0.014	0.10	0.589	−0.06	0.748
MAP	−0.06	0.621	−0.19	0.130	−0.10	0.571	−0.36	0.035	0.10	0.565	0.01	0.956
PP	−0.04	0.733	0.10	0.428	−0.16	0.374	0.05	0.792	0.06	0.746	0.18	0.310
FBG	−0.31	0.017	−0.20	0.117	0.01	0.956	0.01	0.974	−0.31	0.126	−0.40	0.044
Weight	0.14	0.248	0.46	<0.001	0.34	0.050	0.56	0.001	0.18	0.306	0.40	0.018
Height	0.15	0.237	0.32	0.009	0.33	0.050	0.60	0.001	−0.11	0.518	0.05	0.789
BMI	0.06	0.624	0.28	0.019	0.22	0.212	0.25	0.157	0.22	0.211	0.34	0.047
MoCA-B			0.24	0.044			0.35	0.041			0.18	0.300
T	0.24	0.044			0.35	0.041			0.18	0.300		

MoCA-B: Montreal cognitive assessment-basic, T: serum total testosterone, SBP: systolic blood pressure, PP: pulse pressure, DBP: diastolic blood pressure, MAP: mean arterial blood pressure, FBG: fasting blood glucose, BMI: body mass index

Table 4: Predictors of MCI among the participants

Variable				95% CI for β		
	B	S.E.	β	Lower	Upper	P
Age	−0.061	0.035	0.940	0.877	1.008	0.083
Sex	−0.353	0.808	0.703	0.144	3.422	0.662
Marital status	1.951	1.080	7.034	1.847	58.380	0.041
Level of education	1.682	0.787	5.376	1.150	25.134	0.033
Level of testosterone	−1.805	0.727	0.164	0.040	0.683	0.013

Table 5: Predictors of MCI among T2D patients

Variable	B	S.E.	β	95% CI for β		p
				Lower	Upper	
Age	0.018	0.044	1.019	0.934	1.111	0.679
Sex	−4.046	2.008	0.017	0.000	0.896	0.044
Annual income	−1.700	2.148	0.183	0.003	12.315	0.429
Education	−0.422	0.201	0.656	0.442	0.971	0.035
Level of testosterone	−0.331	0.966	0.718	0.108	4.771	0.732

proportion of those with low annual income, low level of formal education, and lack of spousal relationship.

Despite reported association between T2D and blood pressure in the literature, no association between T2D and blood pressure categories was found. Equally, none of the blood pressure parameters differed between the T2D patients and controls. This finding of normal blood pressure among T2D patients is similar to what we have reported in another cohort of T2D patients from the same environment.[24] This could be due to the fact we excluded those with hypertension from the study; it could also be due to the fair glycemic control among the T2D patients (mean FBG = 8.79 mmol/L). The serum total testosterone did not differ among male T2D patients and male controls but female T2D patients had significantly lower serum total testosterone compared to female controls. Similarly, more than 50% of both T2D patients and controls had low levels of serum total testosterone, though low levels of serum testosterone were not statistically significantly associated with T2D. This finding of no significant relationship between T2D and low level of total testosterone contradicts that of a number of studies. A low level of testosterone has been found to be independently associated with insulin resistance and hence T2D.[10] In a systematic review and meta-analysis of 56 studies, Zhang *et al.* found decreases in both total and free testosterone in adult male T2D patients;[7] and a 2-year testosterone supplementation trial reduced the proportion of participants with T2D in a study that compared the efficacy of testosterone and traditional lifestyle modification in the treatment of T2D. Even though there was no statistically significant difference in serum total testosterone between T2D patients and controls in this study, a high proportion of those with low serum total testosterone in both groups suggested a possible relationship between low testosterone and T2D among the participants. The high proportion of those with low serum testosterone among the controls could be due to their older age, while that among the T2D patients due to the effect of T2D. Indeed, serum total testosterone was negatively correlated with age among the controls but not among the T2D patients, implying that the controls had age-related low serum testosterone, while the T2D patients had T2D-related low serum testosterone.

In order to assess possible influence of some characteristics of the participants on cognitive function, the participants were divided into cognitively normal and MCI groups. Then, the differences in some qualitative variables among the two groups and their possible association with MCI were assessed. MCI was statistically significantly associated with being female, low level of formal education, lack of spousal relationship, low level of annual income, and normal or higher level of serum total testosterone. Indeed, sex, marital status, and level of education were the significant predictors of MCI among the participants. A low level of formal education together with a lack of spousal relationship has been reported to be associated with cognitive impairment and dementia among elderly T2D patients in northern Nigeria,[28] the same environment with the participants of this study. In a study of cognitively healthy community-dwelling older persons, Chen *et al.*[29] reported highly educated older persons to have better performance in multidomain cognitive function. People with high level of formal education are more likely to involve themselves in leisure activities that could stimulate areas of the brain involved in cognitive function. Similarly, spousal relationship provides better social interaction and emotional stability and hence better cognitive function. Females in this environment historically have low access to formal education, are less economically empowered, and are more likely to lose spousal relationship due to the death of a spouse. These factors could likely explain the higher proportion of those with MCI among female participants in this study. Mean BMI did not differ between the cognitively normal and MCI groups nor were BMI categories associated with MCI. Indeed, MoCA-B score did not correlate with BMI at any level. This implies that there is no relationship between cognitive function and BMI among both T2D patients and controls. A relationship between cognition and BMI in the literature is mixed, ranging from no relationship, positive relationship, negative relationship, and U- or J-shaped relationship.[13–18] This

finding of no relationship between cognition and BMI therefore fits the growing literature on this field.

Limitations of the study

A relatively small sample size was used and did not match the participants for age and level of education. This could have effect on some of the findings. Despite these limitations, this study has provided data on cognitive impairment in T2D patients and its relationship with serum testosterone and obesity that others can build on.

CONCLUSIONS

Proportion of those with MCI in T2D is high and is associated with female sex, low level of formal education, lack of spousal relationship, and normal or higher levels of serum testosterone. MCI is not associated with overweight or obesity.

Conflict of interest

We have no conflict of interest to declare.

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Case Report

Pelvic space-occupying lesion with lower urinary tract symptoms diagnosed as inflammatory myofibroblastic tumor of the prostate with a review of the literature

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Abstract

Inflammatory myofibroblastic tumor (IMT), a rare type of soft-tissue tumor in the body in the context of the urinary system, is comparatively more common in the kidney and urinary bladder. Prostatic IMT is extremely rare. We report a rare case of a 77-year-old man who presented with lower urinary tract symptoms later diagnosed as IMT of the prostate. A brief review of the literature is discussed.

Keywords: Inflammatory myofibroblastic tumor, malignancy of the prostate, prostatic abscess

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INTRODUCTION

According to the World health organization classification, an inflammatory myofibroblastic tumor (IMT) is defined as a neoplasm with the morphologic character of proliferating spindle cells admixed with variable amounts of a lymphoplasmacytic infiltrate.[1] In the past, they have also been referred to under different titles, including "reactive pseudosarcomatous response," "inflammatory pseudo tumor," "pseudosarcomatous fibromyxoid tumor," "pseudosarcomatous lesion," and "inflammatory myofibroblastic tumor."[2-4] With the advancement of immunohistochemistry, it was found that an alteration of the anaplastic lymphoma kinase (ALK) gene was evident in such bladder lesions. These lesions are now considered the result of neoplastic transformations rather than reactive processes, and the name IMT has been preferred.[4,5] Prostate IMT is rare, and only nine cases have been recorded in the English literature since it was first reported in 1984 as an atypical fibromyxoid tumor. The purpose of this study was to examine the clinical and pathological characteristics of prostate IMT and particularly to identify previous histories of injury and the prognostic differences of prostate IMT in relation to ALK expression by reviewing case reports and the relevant literature.

CASE REPORT

A 77-year-old gentleman was admitted with complaints of difficulty in micturition for the last 4 months and was previously admitted to the hospital with acute urinary retention. A periurethral catheter was placed, and large

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seminal vesicle cyst drainage was done transrectally through a pigtail catheter. The patient now had right scrotal swelling and perurethral purulent discharge. The patient was a k/c/o type 2 diabetes mellitus on medication. Physical examination revealed no positive findings, with no boggy swelling and non-tender, non-nodular grade 3 prostatomegaly on digital rectal examination. The patient was evaluated for the above complaints and found to have a large rectovesical space-occupying lesion (SOL) (possibility of prostatic abscess). Blood investigations showed mildly raised prostate-specific antigen (6.18 ng/mL) and erythrocyte sedimentation rate with a normal white blood count. A urine examination revealed plenty of pus cells with a culture positive for *Enterococcus faecalis*. The ultrasonography report was suggestive of an enlarged prostate gland of 300 g with a postvoid residual volume of 53 mL and a multifocal abscess in the prostate (5 × 6 cm). In uroflowmetry, the patient recorded a voided volume of 162 mL with a Q_{max} of 3.9 mL/s. Impression of contrast-enhanced computed tomography report was prostate, and seminal vesicle is compressed with anterior displacement of the seminal vesicle, thick-walled SOL with the air-fluid level of size 10 × 10 × 11 cm in the rectovesical space with loss of normal outline of prostate and small compressed part of prostate seen inferior to the SOL [Figure 1]. Magnetic resonance imaging (MRI) pelvis reported a large SOL with heterogeneous signal in rectovesical space of size 10.4 × 10.9 × 11 cm with the prostate and seminal vesicle compressed and anteriorly displaced. The prostate was seen as inferior to the SOL. Transrectal ultrasound scan-guided aspiration of the SOL was done and sent for culture and cytology, which revealed degenerated cells with polymorphs and no atypical cells suggestive of acute inflammation with no organism in culture. Exploratory laparotomy with excision of the extraperitoneal retrovesical mass was done. The intraoperative and postoperative courses were uneventful. Intraoperatively, on cystopanendoscopy, a false tract of 4 cm with a blind end was seen just right to the ejaculatory duct opening, and on exploratory laparotomy, a 15 × 12 cm extra peritoneal retrovesical cystic mass with a solid component and capsular wall adherent posteriorly with the rectum and anteriorly with the urinary bladder was noted, which had purulent material in it [Figure 2A]. Dissection was done by making a plane between the cyst and capsule, and the cyst was removed except for the part attached to the rectum. On gross histopathological examination, a circumscribed mass with myofibroblastic spindle cell proliferation was seen. The background

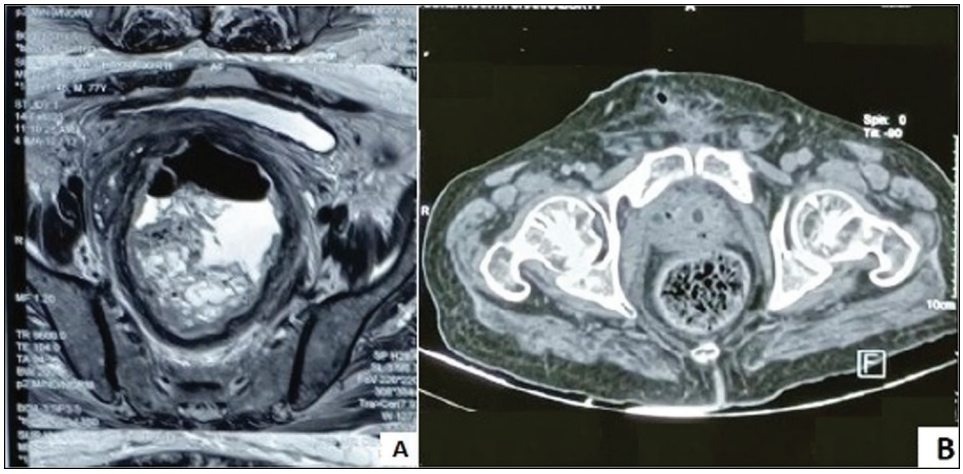

Figure 1: MRI pelvis and CECT pelvis—large SOL with heterogenous signal in rectovesical space of size 10.4 × 10.9 × 11 cm

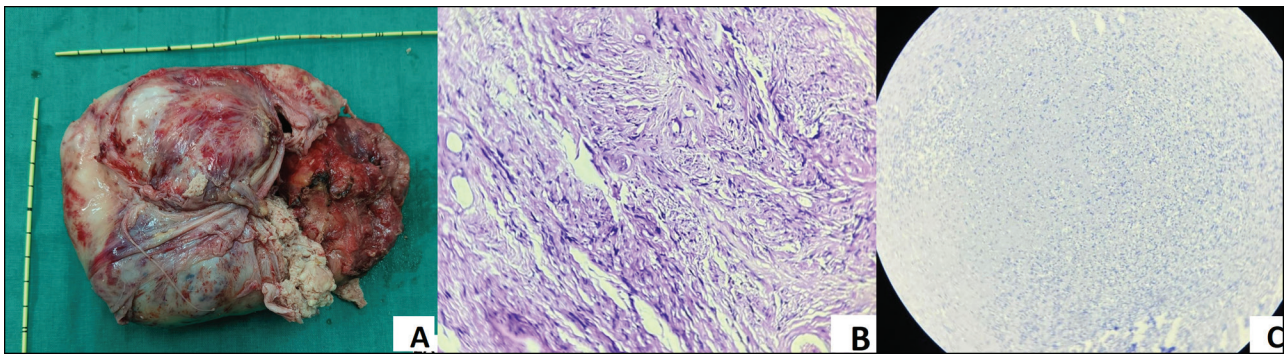

Figure 2: Intraoperative (A), H&E image (B), immunohistochemistry (C) image

showed mixed inflammatory cell infiltration with loose and oedematous stroma. Multiple cross-sections of the urethra with a prominent muscular wall along with prostatic parenchyma were identified. Mitotic figures were scanty [Figure 2B]. Occasional areas of hyalinization are seen in the stroma. On immunohistochemistry, Vimentin was strongly positive, while Desmin was focally positive. ALK [Figure 2C], S100, Myoglobin, and CD117 immunohistochemistry (IHC) were completely negative. The Ki67 labeling index was 10% (low proliferation). Considering typical clinicopathological findings, the tumor was further tested for ALK gene rearrangement (2p23) by FISH with a break-apart probe. The ALK test was negative.

DISCUSSION

IMT is a rare disease primarily originating in soft tissues. A dozen cases of IMT prostate have been discussed, but the etiology still remains unclear. Causative factors may include viral (HHV-8, EBV) or bacterial infection and the body's response to trauma and surgical tissue injury. Recently, ALK-positive findings with a common 2p23 rearrangement were observed in 40%–60% of IMTs, reflecting it to be a true neoplasm. On review of the cases of prostatic IMT reported in the English literature, it was found to occur in various age groups (21–83 years old) but commonly in the elderly (mean age = 60.8 years). The chief complaint of patients was urinary obstruction symptoms, which were occasionally accompanied by hematuria or fever. In some patients, there was difficulty accurately assessing the size of the tumor because, although the tumor was diagnosed through transurethral resection of the prostate and transperineal biopsy, the diameters ranged from 1.2 to 6.5 cm. ALK gene alterations were detected by fluorescence *in situ* hybridization (FISH) in 13 (72%) of the 18 tested cases, including two with injuries from previous procedures. Thirteen (72% of the 18 tested cases) showed agreement between FISH ALK results and ALK protein results by immunohistochemistry in the IMT of the urinary tract. In addition, 5 out of the 10 cases found to be ALK-negative by IHC were found to have ALK gene alterations by FISH, while all eight ALK-positive cases by IHC (100%) had FISH ALK gene alterations. Recurrences were reported to have no association with ALK alterations. As in our case, the patient was initially treated as a prostatic abscess, but finally, on histopathological examination, it was found to be an inflammatory myofibroblastic tumor, and on IHC, Vimentin was strongly and diffusely positive, Desmin was focally positive, S100 was negative, ALK was negative, and Myogenin was negative. CD117 was negative.

CONCLUSION

If a spindle-cell lesion with inflammatory cells is observed in the biopsy sample from a patient with a previous history of inflammation or abscess, IHC must be conducted for α-smooth muscle actin, CD10, CD34, Desmin, and ALK in considering the possibility of IMT, and a FISH ALK test should be considered if ALK is negative in the IHC examination. This case of IMT may be further tested for ROS1 and PDGF-RB alterations. ETV6-NTRK3 fusion may also be looked for. Since, in our case, the KI-67 index (10%) denotes low proliferation, the neoplasm has to be considered benign, and the patient is kept on regular follow-up.

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Conflicts of interest
There are no conflicts of interest.

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Case Report

Abdominal hysterectomy due to uterine rupture causing bilateral ureterovaginal fistula: A rare case report

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Abstract

Ureterovaginal fistula (UVF) is defined as abnormal communication between ureter and vagina. Although documented after radical hysterectomy, post radiation and retained pessary incidence of bilateral UVF is still very rare. We have documented a case report of a multipara woman presented with persistent urinary leakage following an emergency hysterectomy for obstructed labor. After evaluation with imaging there was bilateral hydroureterophrosis with dense purulent collection mixed with contrast in the vesicular area with lower end of ureter draining in the vaginal vault with preserved renal function. During exploration both ureters were dilated. Instillation dye in both ureters showed extravasation in vagina. After ligating distal ends modified Lich-Gregoir technique done over double J (DJ) stents. DJ removed after 3 months. Bilateral UVF is only 5%–10% of all ureteric injury. Aggressive blind clamping, excessive hemorrhage, distorted anatomy, malignancy and surgeons experience play a crucial role. Obstetric cause is the prime factor. Preventing measures like proper screening of antenatal patients, early detection of high-risk pregnancy, supervised caesarean section should be taken to avoid ureteric injuries

Keywords: Bilateral ureterovaginal fistula (UVF), computed topography (CT), double J (DJ), intrauterine fetal death (IUFD), per-urethral catheter (PUC)

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INTRODUCTION

Ureterovaginal fistula (UVF) after intraoperative ureteric injury is one of the important iatrogenic complications of gynecological surgeries. Documented incidence of UVF is approximately 0.5%–2.5% after gynecological surgeries [1,2]. Benign diseases contribute approximately 0.1%–1.5% and it is increased up to 5% gynecological malignancy due to intraoperative adhesion. Approximately 30%–45% ureteric injuries are detected intraoperatively and 55%–70% injuries are discovered in postoperative periods. The relative occurrence of UVF is due to hysterectomy, ovarian tumor excision, pelvic lymphadenectomy, oophorectomy, adhesiolysis and drainage of lymphocele with some nonsurgical cause like endometriosis, Crohn's disease, post-radiation therapy [3]. Hysterectomy remains the leading cause of ureteric injury causing UVF nevertheless surgeon experience plays a crucial role.

In spite of documentation of various etiologies of ipsilateral UVF, the incidence of bilateral UVF prevails to

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be extremely rare. Some literature documented bilateral UVF after radical hysterectomy, post radiation and retained pessary but incidence of bilateral iatrogenic UVF following an emergency abdominal hysterectomy due to uterine rupture has not been documented in published literature.

CASE REPORT

A 23-year-old woman P3 + 0 presented to urology department of a tertiary care hospital with persistent urinary leakage for 3 months following an emergency hysterectomy for uterine rupture with intrauterine fetal death (IUFD). During hysterectomy and adhesiolysis intraoperative bladder injury was noted and repaired. An abdominal drain and perurethral Foley's catheter (PUC) of 16 Fr. was placed. Patient was stable in postoperative period with PUC *in situ*. After 7th POD patient had involuntary passage of urine pervaginum with decreased urine output through PUC. After removal of PUC patient had persistent involuntary leakage of urine from pervaginum with no history of normal voiding. On pervaginal examination there was continuous urinary leakage although no definite fistulous tract was found. 3 swab test was negative. Cystoscopy revealed bladder mucosa to be edematous and congested with no obvious fistulous opening. Ureteric opening of both sides was localized but guidewire could not be negotiated. Computed topography (CT) scan after 1 month showed bilateral hydroureterophrosis with dense purulent collection mixed with contrast in the vesicular area with lower end of ureter draining in the vaginal vault. On follow up computed CT scan it was revealed that a cystic lesion measuring 3.9 cm × 3.7 cm in axial plane with thin 1 mm enhancing walls without internal septation was seen in relation to right adnexa with adjacent long tubular structures likely to be urinoma draining from both the ureter. The vaginal cavity was opacified by the contrast in the delayed phase of the study with direct fistulous communication with the bilateral ureters [Figure 1]. The bilateral lower ureter also showed short segment strictures with post obstructive bilateral hydroureteronephrosis with preserved renal function [Figure 2]. On exploration both ureters were found to be hugely dilated and tortuous. On table injection of betadine and methylene blue into the dilated ureters respectively shows staining of vagina. Distal part of dilated ureter of both the sides are ligated as low as possible and proximally mobilized. Both ureters are reimplanted by modified Lich-Gregoir technique with tension free, mucosa to mucosa water tight anastomosis over 5/26 Fr. Double J (DJ) stent. Patient postoperative recovery was uneventful with no passage of urine pervaginum. Patient was discharged with PUC and bilateral DJ stent *in situ*. Catheter was removed after 3 weeks and patient passed urine through perurethral route. After 3 months DJ stent of both sides were removed. The follow-up after 3 months revealed no signs of hydronephrosis on ultrasonography. Pervaginal examination revealed no leakage of urine.

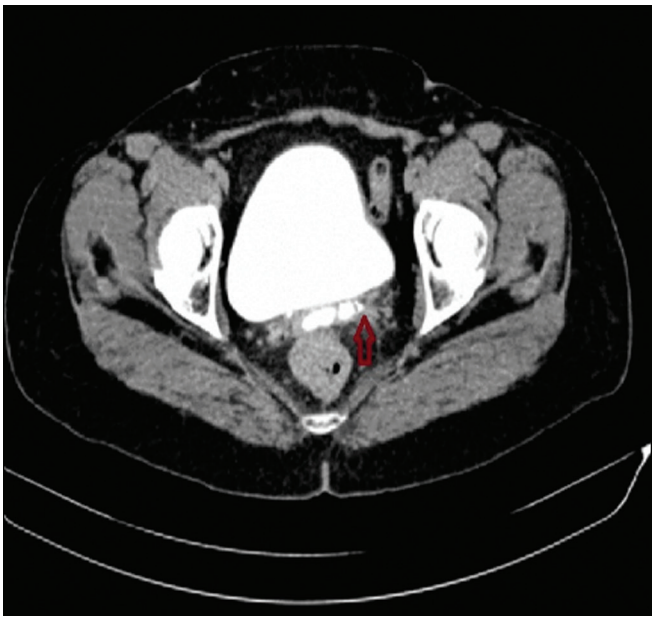

Figure 1: Delayed excretory films suggested contrast filled tract in vaginal vault

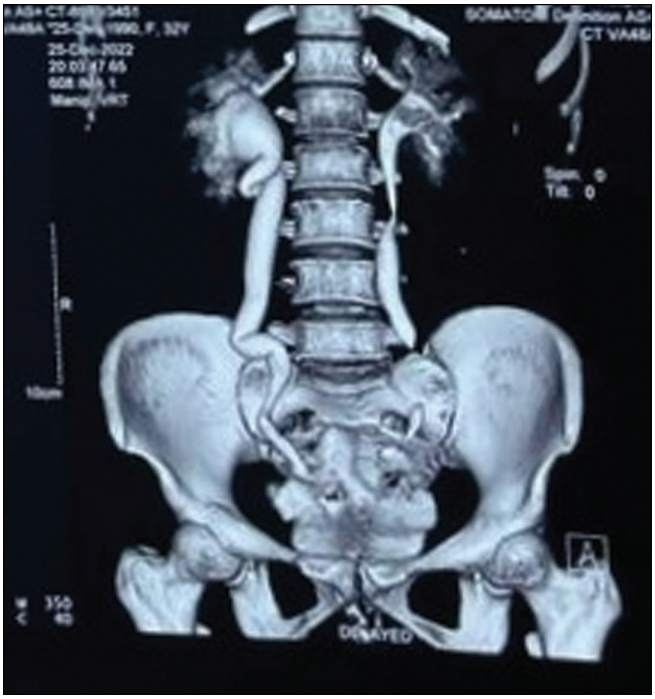

Figure 2: Reconstructive view of shows dilated and tortuous both ureters

DISCUSSION

Bilateral UVF is due intraoperative ureteric injury during pelvic gynecological surgery with a reported incidence of

0.5%–1.5% [4]. Bilateral ureteric injury is documented to be 5%–10% among all ureteric injuries. The predisposing factors are excessive intraoperative hemorrhage leading aggressive blind clamping and cautery, malignancy with adhesion and distorted anatomy, pelvic inflammatory disease. Preoperative assessment on contrast enhanced CT scan clearly demarked extravasation of contrast in vaginal vault with communication with both ureters. Both preoperative imaging and intraoperative dye test were sufficient to confirm bilateral fistulous communication between ureter and vagina.

Patient with bilateral UVF usually experience continuous dribbling of urine per vagina within 1–4 weeks of surgery with flank pain, fever due to obstruction and infection complicated by deteriorating renal function with sepsis. Intraoperatively detected injuries can be managed with repair with stents. Delayed diagnosis of ureteric injuries with UVF, deranged renal function and urosepsis may lead to significant mortality and morbidity [5]. The primary aim in early management of UVF is to control infection and early preservation of renal function. In case of poor general condition and to avoid morbidity of patient a percutaneous nephrostomy or a DJ stent can be placed. Literature reviewed early DJ stenting for 6–8 weeks is beneficial for fistula closure but, in our case both ureteric orifices were failed to be cannulated [6]. Complex ureteric strictures with fistula can be managed by ureteroureterostomy, ureteroneocystostomy or ileal interposition or autografts by open, laparoscopic and robotic method. Most of the ureteric injury involves lower end of ureter near pelvic brim allowing ureteroneocystostomy. We have performed open ureteric reimplantation by Lich-Gregoir technique. More proximal or complex fistula requires bladder reconstruction or urinary diversion. Our patient had an uneventful recovery and catheter removed after 3 weeks although literature suggested early catheter removal within 2 weeks has successful outcome.

CONCLUSION

Morbidity due to ureteric fistula is far-reaching as it is an iatrogenic cause leading to prolonged hospital stay, poor surgical outcome, deteriorating renal function and need of re-exploration. Obstetric cause found to be the most inciting factor for gyneurological fistula. Preventive measures should be taken by proper screening of antenatal patients, early detection of high-risk pregnancy, supervised caesarean section with careful selection of patients for hysterectomy.

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Conflicts of interest
There are no conflicts of interest.

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Case Report

An unusual cause of osteomalacia in a young lady

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Abstract

Oncogenic osteomalacia is a rare entity, caused by excessive secretion of fibroblast growth factor-23 (FGF-23) from the peripherally located benign tumours of mesenchymal origin. Patients usually present with chronic widespread pain and fatigue. Diagnostic approach involves demonstration of excessive urinary loss of phosphate and the high plasma level of FGF-23. Whole of PET-CT scan or whole body MRI scan are used to detect the tumour. PET/CT Ga-68 dotatate scan is required often when the other imaging modalities fail to detect the neoplasm. Here we present the case of a 32year old lady who presented to us with chronic low back pain and thorough evaluation helped us to diagnose this rare disease.

Keywords: Fibroblast growth factor-23, low-back-pain, osteomalacia

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INTRODUCTION

Tumor-induced osteomalacia (TIO) or oncogenic osteomalacia, is a rare paraneoplastic syndrome of abnormal phosphate and vitamin metabolism caused by typically small endocrine tumors of mesenchymal origin that secrete the phosphaturic hormone and fibroblast growth factor-23, (FGF-23).[1] Patients usually present with muscle weakness, myalgia, and severe generalized bone aches of long duration, which at times render them bed-bound.[2]

CASE REPORT

We report a case of a 32-year-old lady who presented to us with progressive low back pain without any morning stiffness and both groin pain for the last 2 years. She also complained of aches over the muscles of the upper and lower limbs. For the last 2 weeks, she has been using a stick while walking. There was no history of joint pain, rash, red eyes or fever, loss of appetite, or weight loss.

Examination showed normal vitals and tenderness over bony prominences all over the body with restricted external and internal rotation of the right hip. There were no swollen joints or tenderness at the enthesial points. Systemic examination was unremarkable.

Baseline blood investigations showed normal hemoglobin, normal erythrocyte sedimentation rate and C-reactive protein, normal liver function tests with normal alkaline phosphatase levels [158 IU/L (reference level: 98–250 IU/L)]. X-ray of the pelvis showed looser's zones in both pubic rami and undisplaced fracture of the right femoral neck [Figure 1]. This prompted us to work up for osteomalacia. Investigations showed normal 25-hydroxy vitamin D level (32 ng/mL), normal calcium

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(9.3 mg/dL), low phosphate [1.2 mg/dL (reference level 3.4–4.5 mg/dL)], and normal intact parathormone level [19.8 pg/mL (reference level: 19.6–54.3 pg/mL)]. Urinary concentrations of creatinine and phosphate in a timed sample were 67.5 mg/dL (reference level: 20–320 mg/dL), and 27 mg/dl, respectively. Tubular maximum for phosphate (TmP), corrected for glomerular filtration rate (GFR; TmP/GFR) was 1.2 mg/dL (reference level: 2.6–3.8 mg/dL), suggestive of renal phosphate wasting. Serum calcitriol level was very low [<5 pg/mL (reference level: 19.9–79.3 pg/mL)]. Plasma FGF-23 level came very high [1334.3 RU/mL (reference level: 0–150 RU/mL)] indicative of TIO. Before presenting to us, her primary care physician advised whole body bone scan to evaluate diffuse body pain and it showed increased radiotracer uptake over the sternum—"tie sign"[Figure 2], overgrowth plates around the knee joints and prominent costochondral beadings— "rachitic rosary sign"[Figure 2]. To localize the primary tumor, a whole body magnetic resonance imaging (MRI) scan and whole body fluoro-deoxy glucose positron emission tomography(FDG PET)-CT scan were done but nothing could be found. Next up, we planned for a Galium-68 Dotatate PET-CT scan but could not be performed due to financial constraints. Our final diagnosis was TIO or oncogenic osteomalacia.

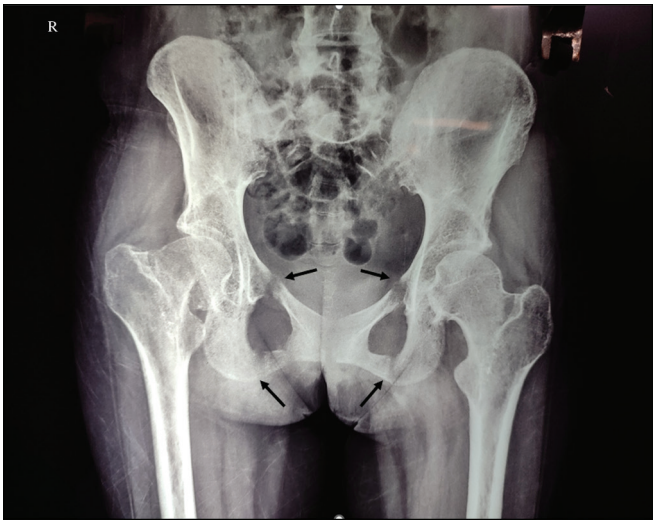

Figure 1: X-ray of the pelvis showing looser's zones (arrows) in both pubic rami and undisplaced fracture in the right femoral neck

The patient was treated with a gradually increasing dose of oral sodium acid phosphate (in four divided dosages) and calcitriol (in two divided dosages). She tolerated a total daily dose of 2 g of elemental phosphate and 2 μg of calcitriol. The orthopedic surgeon opined delayed intervention of fracture till the phosphate level normalizes. Significant symptomatic improvement was achieved after almost a month of therapy with serum phosphate level reaching 2.2 mg/dL.

DISCUSSION

TIO) is a rare paraneoplastic syndrome, in which patients present with bone pain, fractures, muscle pain all over the body, and muscle weakness.[3] The cause is high blood levels of the phosphate and vitamin D-regulating hormone, FGF-23.[4] In TIO, FGF23 is secreted by mesenchymal tumors that are usually benign, but are typically very small and difficult to locate. FGF-23 acts primarily at the renal tubule and impairs phosphate reabsorption and 1α-hydroxylation of 25-hydroxyvitamin D, leading to hypophosphatemia and low levels of 1, 25-dihydroxy vitamin D.[5] A step-wise approach utilizing functional imaging (F-18 fluorodeoxyglucose positron emission tomography and octreotide scintigraphy) followed by anatomical imaging (computed tomography and/or MRI),

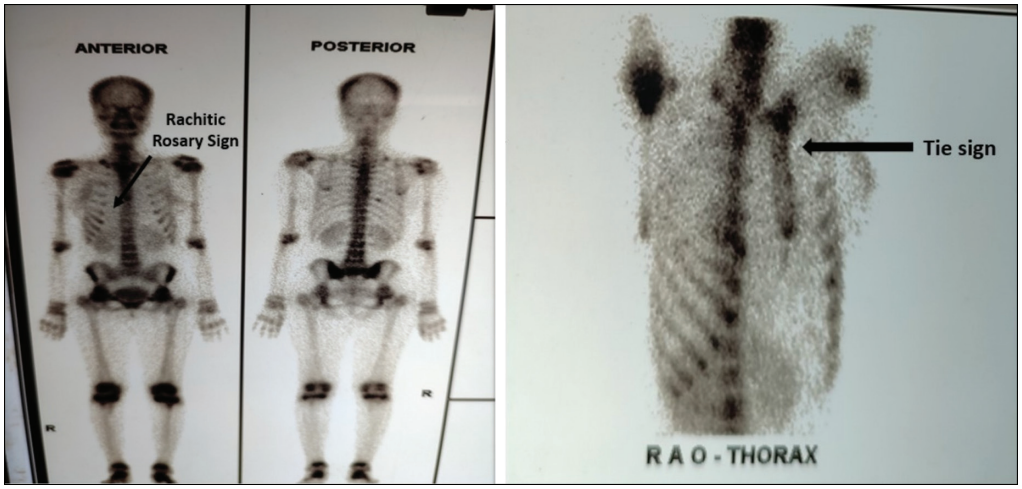

Figure 2: Whole body bone scan images showing increased radiotracer uptake at costochondral junctions, body of sternum, and over-growth plates

and, if needed, selective venous sampling with measurement of FGF-23 is usually successful in locating the tumors. In about 19% of cases, tumors can be localized.[3] Isotope bone scan often reveals characteristic rachitic rosary sign or tie sign or increased radiotracer uptake at growth plates known as "pseudo-reactivation."[2] Burosumab is the only drug approved for TIO and it acts by blocking the FGF-23 receptor. Definite therapy for TIO is the removal of the primary tumor. If tumors cannot be located, medical treatment with phosphate supplements and active vitamin D (calcitriol or alfacalcidol) is usually successful; however, this medical regimen is associated with complications, especially gastric intolerance.[6]

CONCLUSION

Though hypophosphatemia is a common cause of osteomalacia, TIO is a rare entity. Stepwise evaluation is necessary for diagnosing this condition. Functional as well as anatomical imaging modalities are to be ordered for proper localization of the tumor. Whole body FDG PET-CT scan often fails to localize these benign tumors because of their low metabolic activity. Medical management alone can cause significant symptomatic improvement if the dose of phosphate and active vitamin D supplementation is carefully titrated.

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Conflicts of interest

There are no conflicts of interest.

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